IBEC ANNUAL REPORT

2018 Research and services

IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA SEVERO OCHOA

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OCHOA

Contents

2018 in review: People

Groups at a glance 2018

In 2018, IBEC had 21 research groups. Groups leaders are listed here.

More information about the groups and their publications can be found on page numbers shown above the pictures.

Nanoscopy for nanomedicine – Lorenzo Albertazzi

Protein phase transitions in health and disease – Benedetta Bolognesi

Mechanics of development and disease – Vito Conte

Biomaterials for regenerative therapies – Elisabeth Engel

Nanomalaria (joint group IBEC/ISGlobal) – Xavier Fernandez-Busquets

Nanoscale bioelectrical characterization – Gabriel Gomila

Nanoprobes and nanoswitches – Pau Gorostiza, Fausto Sanz

Biomedical signal processing and interpretation – Raimon Jané

Signal and information processing for sensing systems – Santiago Marco

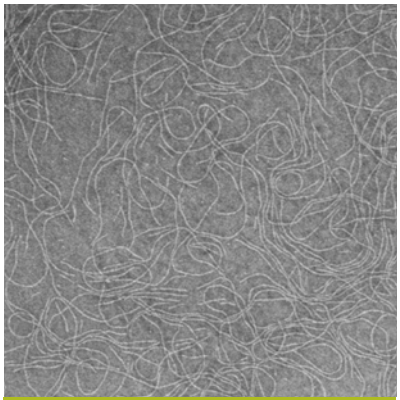
Nanoscopy for nanomedicine
Lorenzo Albertazzi

The main goal of our group is to use Super Resolution Microscopy (nanoscopy) to visualize and track in living cells and tissues self-assembled nanomaterials with therapeutic potential (nanomedicine).

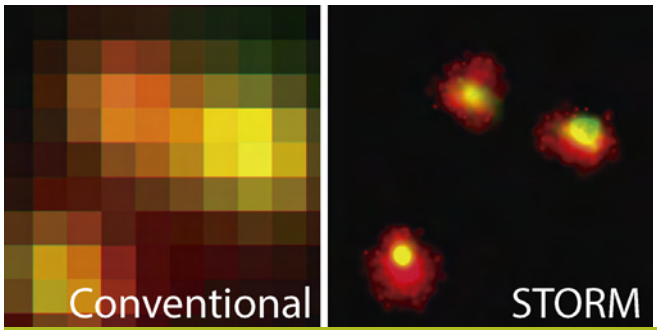
The understanding of materials-cell interactions is the key towards the development of novel nanotechnology-based therapies for treatment of cancer and infectious diseases. Our group aims to use a multidisciplinary approach, at the interface of chemistry, physics and biology, to develop novel nanomaterials for the treatment of cancer and infectious diseases.

We aim at the development of novel nanocarriers for drug delivery based on self-assembly, i.e. able to build themselves. Molecular self-organization is ubiquitous in the biological world and represents for us a source of inspiration for the design of nanostructures with biomedical potential. In particular we focus on the development of self-assembled nanoparticles and nanofibers able to selectively target diseased cells and deliver locally therapeutic moieties such as drugs and genetic material (e.g. DNA, siRNA, mRNA).

Point towards the development of novel nanotechnology-based therapies is the understanding of the behavior of nanomaterials in the complex biological environment. Here we use super resolution microscopy to track nanomaterials during their voyage in the biological environment and to visualize the interactions with blood components, immune system and target cells. We make use of a variety of super resolution techniques based on single molecule detection such a stochastic optical reconstruction microscopy (STORM), photoactivated localization microscopy (PALM), point accumulation for imaging in nanoscale topography (PAINT), and single particle tracking (SPT). These methods allow to achieve a resolution down to few nanometers and are therefore ideal to visualize nanosized synthetic objects in the biological environment. Super resolution microscopy provides a molecular picture of structure-activity relations and represents a guide towards the design of innovative materials for nanomedicine.



TEM image of novel self-assembled nanofibers synthesized in the group.



Nanoparticles interactions with blood components imaged with conventional optical microscopy (left) and super resolution STORM microscopy (right).

Postdocs
Pietro Delcanale

PhD students
Natàlia Feiner
Roger Riera
Teodora Andrian
Maria Arista
Edgar Fuentes
Adrianna Glinkowska
Madhura Vijay Murar
Rodica Alis Olea

Senior researcher
Silvis Pujals

Masters students
Adrian Chetrusca
Sheila González

Undergraduates
Kamila Bohacova

RESEARCH PROJECTS

NANOSTORM Design of Nanomaterials for Targeted Therapies Guided by Super Resolution Imaging
PI: **Lorenzo Albertazzi** | *ERC Starting Grant*

TARGETSTORM Nanomateriales para terapias dirigidas contra el cáncer visualizados con microscopia de súper resolución STORM (2016-2019)
PI: **Lorenzo Albertazzi** | *MINECO Retos investigación: Proyectos I+D*

NANOVAX Nanovacunas diseñadas para inmunoterapia antitumoral MINECO Acciones de Programación Conjunta Internacional
PI: **Lorenzo Albertazzi/Josep Samitier** | *MINECO Retos investigación: Proyectos I+D*

Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
PI: **Lorenzo Albertazzi** | *Obra Social La Caixa*

THERACAT BIO-orthogonal catalysis for cancer therapy
PI: **Lorenzo Albertazzi** | *European Commission. MARIE CURIE - ITN/765497*

SGR Grups de recerca consolidats 2017-2019
PI: **Silvia Pujals** | *AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1536*

PUBLICATIONS

Patiño, T., Feiner-Gracia, N., Arqué, X., Miguel-López, A., Jannasch, A., Stumpp, T., Schäffer, E., Albertazzi, L. and Sánchez, S. Influence of enzyme quantity and distribution on the self-propulsion of non-Janus urease-powered micromotors. Journal of the American Chemical Society, 140 (25): 7896-7903 (2018).

Liu, Y., Pujals, S., Stals, P. J. M., Paulöhrl, T., Presolski, S. I., Meijer, E. W., Albertazzi, L. and Palmans, A. R. A. Catalytically active single-chain polymeric nanoparticles: Exploring their functions in complex biological media. Journal of the American Chemical Society, 140 (9): 3423-3433 (2018).

Delcanale, P., Miret-Ontiveros, B., Arista-Romero, M., Pujals, S. and Albertazzi, L. Nanoscale mapping functional sites on nanoparticles by Points Accumulation for Imaging in Nanoscale Topography (PAINT). ACS Nano, 12 (8): 7629-7637 (2018).

Nanoscopy for nanomedicine

COLLABORATIONS

- **Roey Amir**, Tel Aviv University, Israel
- **Mika Linden**, Ulm University, Germany
- **Ilja Voets**, Eindhoven University of Technology, The Netherlands
- **Giovanni Pavan**, SUPSI, Switzerland
- **Bruno De Geest**, University of Ghent, Belgium
- **Salvador Borros**, IQS Barcelona, Spain

EQUIPMENT AND TECHNIQUES

- Nikon NSTORM Super Resolution Microscope
- Super Resolution microscopy
- Nikon NSTORM Super Resolution Microscope
- Single particles tracking
- TIRF fluorescence imaging

Ardizzone, A., Kurhuzenkau, S., Illa-Tuset, S., Faraudo, J., Bondar, M., Hagan, D., Van Stryland, E. W., Painelli, A., Sissa, C., Feiner, N., Albertazzi, L., Veciana, J. and Ventosa, N. Nanostructuring lipophilic dyes in water using stable vesicles, quatsomes, as scaffolds and their use as probes for bioimaging. Small, 14 (16): 1703851 (2018).

Krivitsky, A., Polyak, D., Scomparin, A., Eliyahu, S., Ofek, P., Tiram, G., Kalinski, H., Avkin-Nachum, S., Feiner Gracia, N., Albertazzi, L. and Satchi-Fainaro, R. Amphiphilic poly(α)glutamate polymeric micelles for systemic administration of siRNA to tumors. Nanomedicine: Nanotechnology, Biology, and Medicine, 14 (2): 303-315 (2018).

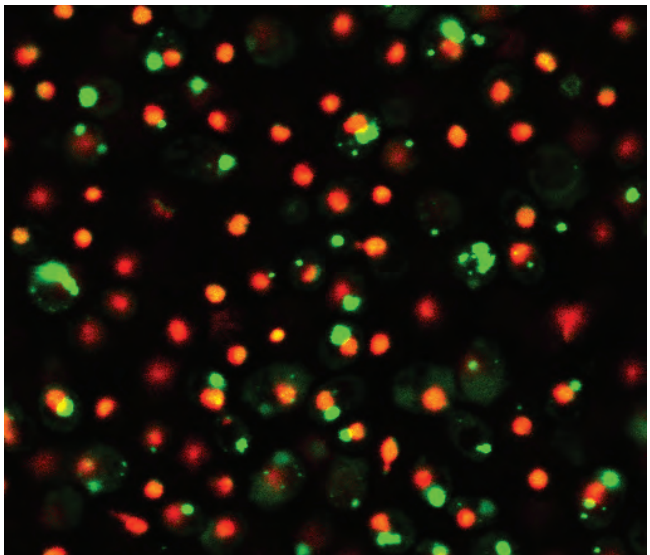
Casellas, N. M., Pujals, S., Bochicchio, D., Pavan, G. M., Torres, T., Albertazzi, L. and García-Iglesias, M. From isodesmic to highly cooperative: Reverting the supramolecular polymerization mechanism in water by fine monomer design. Chemical Communications, 54 (33): 4112-4115 (2018).

van Elsland, D. M., Pujals, S., Bakkum, T., Bos, E., Oikonomeas-Koppasis, N., Berlin, I., Neefjes, J., Meijer, A. H., Koster, A. J., Albertazzi, L. and van Kasteren, S. I. Ultrastructural imaging of salmonella-host interactions using super-resolution correlative light-electron microscopy of bioorthogonal pathogens. ChemBioChem, 19 (16): 1766-1770 (2018).

Protein phase transitions in health and disease
Benedetta Bolognesi

Potentially all proteins can aggregate into insoluble fibrils. Protein aggregates are functional in several contexts, but they are also associated to pathogenesis in a number of severe conditions, such as Parkinson's disease or Amyotrophic Lateral Sclerosis. The concept of protein aggregation has mainly been associated to the formation of insoluble amyloid fibrils, but we now have evidence of the existence of other types of protein assemblies. Dynamic reversible assemblies, for example, are formed by proteins containing prion-like domains through a process of liquid de-mixing in the cytoplasm.

Prion-like domains are low complexity domains which resemble in composition the infectious yeast prions, i.e. they are enriched in asparagine, glutamine, tyrosine and glycine. Typically, prion-like domains are intrinsically disordered but they have the ability to switch to different, more structured conformations. Mutations in these domains are associated to the onset of many neurodegenerative conditions. Importantly, prion-like domains are able to populate multiple physical states: diffuse, liquid de-mixed, insoluble amyloid. Pathological mutations affect these equilibria in ways we cannot yet fully understand, or predict.



TDP-43 GFP Protein Assemblies in S.cerevisiae (mCherry nuclear staining).

Different Amyloid-Beta fibrillar structures imaged by AFM

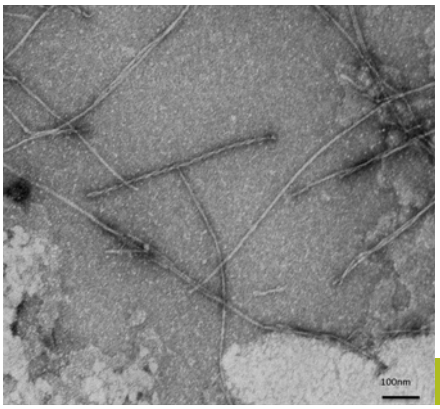
Our lab focuses on understanding how protein sequence determines formation of liquid states versus insoluble aggregates. We have established a systematic approach to elucidate how these alternative states can translate into different phenotypes, and to understand if one particular physical state can be linked to pathology. Finally, we are also interested in the specific mechanisms by which different types of protein assemblies drive pathogenesis.

Protein phase transitions in health and disease

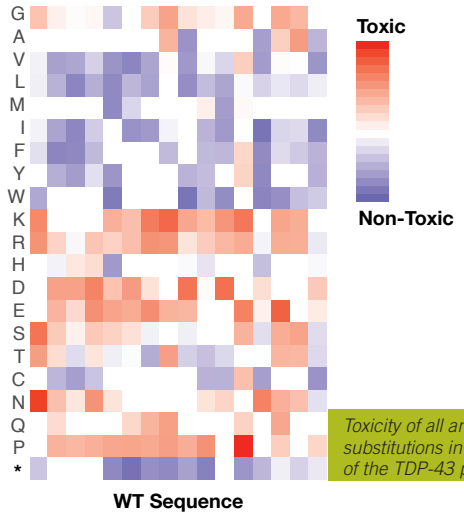
Postdocs
Paola Labarbuta

Masters students
Marta Badia

Research Assistant
Mireia Seuma



Amyloid-Beta fibrils imaged by Electron Microscopy.



Toxicity of all amino acid substitutions in a 16 aa region of the TDP-43 prion-like domain.

We address these questions by coupling deep mutational scanning to high-resolution biophysics. We use a S. cerevisiae model to simultaneously evaluate the fitness effect of thousands of mutations within disordered protein domains implicated in disease and generate a genotype-to-phenotype map for each of them. We then use a similar high-throughput strategy to measure the effect of the same set of mutations on the physical state of the proteins (diffuse, liquid de-mixed, insoluble). This systematic approach allows us to choose mutations with specific effects on fitness and physical state for further characterization by in vitro biophysics in order to formulate more rational hypothesis on the mechanisms involved in protein-induced toxicity.

COLLABORATIONS

- **Ben Lehner,** CRG, Barcelona, Spain
- **Sofia Giorgetti,** University of Pavia, Italy
- **Xavier Salvatella,** IRB Barcelona, Spain
- **Ina Vorberg,** DZNE Bonn, Germany

PUBLICATIONS

Bolognesi, Benedetta, Lehner, Ben. Reaching the limit eLife , 7, e39804 (2018).

Mechanics of Development and Disease
Vito Conte

In the group we advance cross-disciplinary research at the interface between biology, physics and engineering by studying the mechanical biology and the biological mechanics of pathological development and disease progression. Specifically, we focus on soft tissue morphogenesis – the process by which a tissue takes or lose shape.

Deciphering the physical mechanisms of tissue morphogenesis in vivo and in vitro (synthetic morphogenesis) is a powerful expedient to identify new mechanical hallmarks of cancer progression and define principles of tissue design for organ regeneration. This is so because both healthy and pathological tissues take or lose their shape through processes such as folding, segregation, growth, remodelling and invasion. These are biological processes involving mechanical events that require cells to deform, bear or develop forces as well as to fine-tune their material properties. Deciphering these processes in normal and pathological conditions provides experimental data that can be directly translated into therapeutics targeting diseased cells and tissues at the physical level.

To that end, we are developing new multidisciplinary methods to quantify cell and tissue mechanics in arbitrary 2D and 3D environments that have physiologically-relevant properties. These methods hybridise physical, computational and biological approaches to extract mechanical information from large amounts of experimental data in vitro, in vivo and ex vivo. This data used to identify what mechanical quantities can determine and/or predict cells and tissues dynamics in normal and pathological conditions such as those of carcinogenesis and tumour progression.

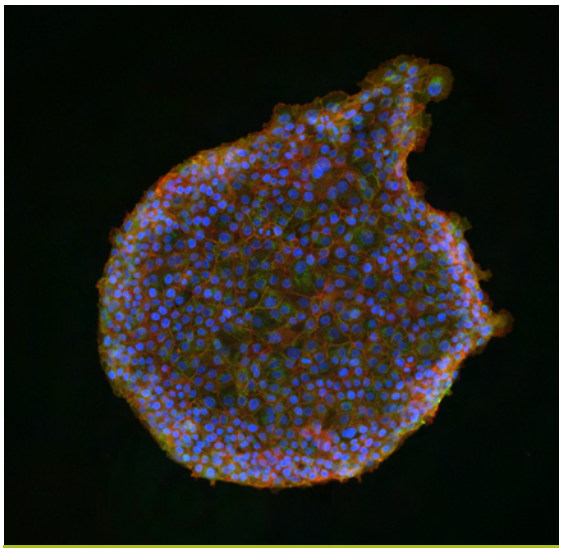


Figure. Human breast epithelium towards malignant transformation. Red – phalloidin, Green – E-cadherin and Blue - DAPI.

PhD student
Giulia Fornabaio

Postdoc researcher
Agata Nyga

RESEARCH PROJECTS

CANCERMECHREG Regulacion biomecanica de la progresion del cancer (2016-2019)
PI: **Vito Conte** | MINECOProyectos I+D Excelencia

COLLABORATIONS

- **Carlijn Bouten,** TU/e, Endhoven, Netherlands
- **Cecilia Sahlgren,** TU/e, Eindhoven, Netherlands
- **Fanny Jaulin,** Gustave Roussy, Paris, France
- **Buzz Baum,** UCL, United Kingdom
- **Jose Muñoz,** UPC, Barcelona, Spain

EQUIPMENT AND TECHNIQUES

- Mechanical quantification in vitro and in vivo
- Experimental physical modelling in silico

PUBLICATIONS

Uroz, M., Wistorf, S., Serra-Picamal, X., Conte, V., Sales-Pardo, M., Roca-Cusachs, P., Guimerà, R. and Trepat, X. Regulation of cell cycle progression by cell–cell and cell–matrix forces. Nature Cell Biology, 20 (6): 646-654 (2018).

Munoz, J. J., Amat, D. and Conte, V. Computation of forces from deformed visco-elastic biological tissues. Inverse Problems, 34 (4): 044001 (2018).

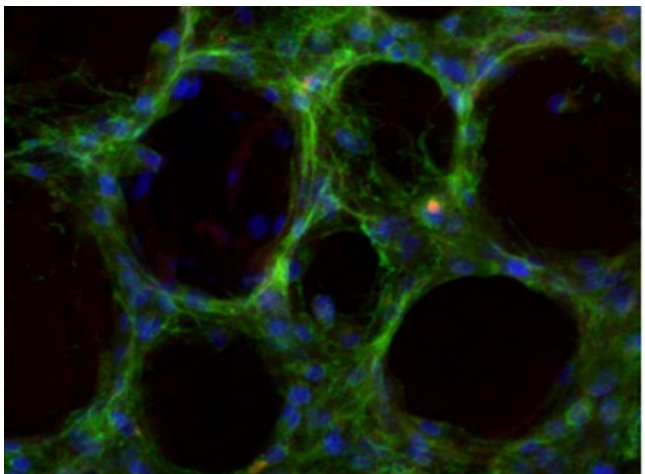
Biomaterials for Regenerative Therapies
Elisabeth Engel

Research in the Biomaterials for Regenerative Therapies group is devoted to the development and knowledge transfer to industry of innovative biomaterials and scaffolds for tissue regeneration.

We design, fabricate and characterize bioactive and biodegradable materials and investigate their interactions with biological entities, both in terms of their fundamental aspects and with specific applications for tissue engineering purposes in mind. The aim is the repair and functional restoration of tissues or organs by means of 3D scaffolds, cells and signals.

Our research is built up in three pillars:

1) Creating microenvironments for tissue regeneration. Understanding the interaction of the designed scaffolds with the cells is the key to induce a regenerative environment. We have developed models that explain the activation of angiogenesis and neurogenesis promotion based on the biomaterials properties and the structure of the scaffold, together with the degradation products that promote a bioactive environment. During 2018 we have studied the activation of progenitor cardiac cells, recruitment and differentiation in response to these scaffolds by means of instructive matrices.



Microtissues formed with dermal fibroblasts.

2) Translating basic research towards new developed products. We are applying Key Enabling Technologies in Biomaterials fabrication to give solutions to companies. A personalized maxillofacial substitute using 3D printing is being developed together with Avinent Implant system, SL. A new dressing that promotes the fast healing of chronic wounds, promoting cell recruitment and regeneration is now under preclinical studies.

3) Disease models. We are developing 3D models for tumor research based on cells self-produced extracellular matrices. These microtissues can be modified to culture cancer cells to simulate an ex vivo tumor that can be used for basic cancer research or drug screening. We are also developing novel bioinks for the fabrication of bioprinted platforms as 3D models and bioengineered constructs. The use of microfluidics simulating a vessel, or a cardiac tissue is another type of model that help to make a step forward on cardiac regeneration.

Biomaterials for Regenerative Therapies

Postdocs
Bárbara Blanco
Cristina Pilar Garrido

PhD students
Sergi Rey
Adrián López
Jesús Ordoño
Gerard Rubí
Irene Cano
Joan Martí

Senior researcher
Miguel Ángel Mateos
Soledad Pérez
Oscar Castaño

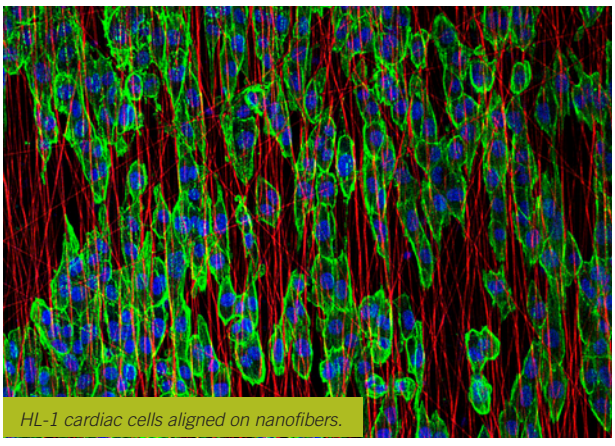
Masters students
Pere Badia
Jaume Bagué
Jose Roberto Barcena
Raisha Lorena García
Gustaf Jonsson
Renato Eduardo Yanac

Visiting researcher
Felipe Andrés Olate

We are participants of the RIS3CAT LLAVOR 3D Community, funded by ACCIO, that aims to accelerate the development and adoption of additive manufacturing and 3D printing technologies by the industry.

We are new members of the Red de Terapia Celular (Tercel) to collaborate with the cell therapy groups in tissue and organ regeneration.

These equipment and services constitute unit U5 of NANBIOSIS, the integrated infrastructure for the production and characterization of nanomaterials, biomaterials and systems in biomedicine, of CIBER-BBN and the Minimal Invasion Surgery Center Jesús Usón, which has been recognized by Spanish Government as Unique Scientific-Technological Infrastructure (ICTS).



HL-1 cardiac cells aligned on nanofibers.

RESEARCH PROJECTS

MatriCell Desarrollo de partículas poliméricas para generar matrices extracelulares in vitro (2016-2019)
PI: **Elisabeth Engel** | *MINECO - Retos investigación: Proyectos I+D/MAT2015-68906-R*

MICARE Creación de microentornos para la regeneración cardíaca in vivo (2017-2019)
PI: **Elisabeth Engel** | *MINECO - Acciones Dinamización Europa Investigación / EUIN2017-89173*

TERCEL Red de Terapia Celular (TerCel)
PI: **Elisabeth Engel** | *ISCIII Redes Temáticas de Investigación Cooperativa en Salud/RD16/0011/0008*

QuirofAM Ecosistema d'R+D+i per la implementació i adopció de la Fabricació Additiva / Impressió 3D a la indústria de Salut (2018-2020)
PI: **Elisabeth Engel** | *ACCIÓ - Acreditació de comunitats RIS3CAT i la selecció de projectes col•laboratius de recerca, desenvolupament i innovació/ COMRDI16-1-0011*

M-Bio4Health Biomarcadores fisiológicos multimodales para la monitorización no-invasiva y cuidado a domicilio de pacientes EPOC con comorbilidades
PI: **Raimon Jané** | *MINECO Retos investigación: Proyectos I+D/DPI2015-68820-R*

PUBLICATIONS

Castaño, O., Pérez-Amodio, S., Navarro, C., Mateos-Timoneda, M. A. and Engel, E. Instructive microenvironments in skin wound healing: Biomaterials as signal releasing platforms. Advanced Drug Delivery Reviews, 129 95-117 (2018).

Navarro-Requena, C., Weaver, J. D., Clark, A. Y., Clift, D. A., Pérez-Amodio, S., Castaño, Ó., Zhou, D. W., García, A. J. and Engel, E. PEG hydrogel containing calcium-releasing particles and mesenchymal stromal cells promote vessel maturation. Acta Biomaterialia, 67 53-65 (2018).

Navarro, C., Pérez-Amodio, S., Castaño, O. and Engel, E. Wound healing-promoting effects stimulated by extracellular calcium and calcium-releasing nanoparticles on dermal fibroblasts. Nanotechnology, 29 (39): 395102 (2018).

COLLABORATIONS

Dr. Ernest Mendoza Applied Nanomaterials Laboratory, Research Centre in Nanoengineering, Technical University of Catalonia (UPC, BarcelonaTech), Spain

Dr. Izabella Rajzer Institute of Textile Engineering and Polymer Materials, University of Bielsko-Biala, Poland

Dr. José María Mora Servei de cirurgia ortopèdica i traumatològica, Consorci Hospital de Terrassa, Spain

Dr. Mercè Alsina Servicio de Dermatología, Hospital Clínic de Barcelona, Spain

Prof. Didier Letourneur Laboratoire de Bioingénierie Cardiovasculaire, INSERM, University Denis Diderot-Paris 7, Paris, France

Prof. Dirk Grijpma, Department of Biomaterials Science and Technology, University of Twente, Twente, the Netherlands

Prof. Francesco Serino Department of Vascular Surgery, Istituto Dermatologico dell'Immacolata (IDI), Rome, Italy

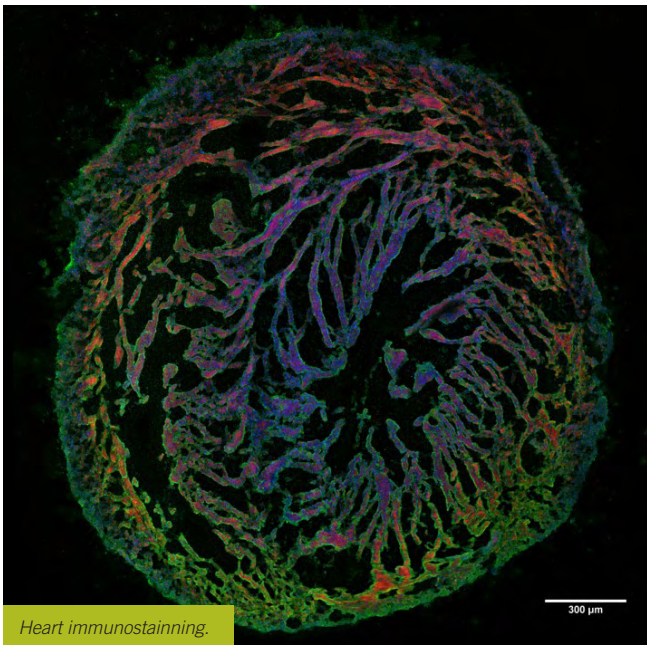
Dr. Jerónimo Blanco Institut de Ciències Cardiovasculars de Catalunya and CSIC, Barcelona, Spain

Dr. Joelle Amedee INSERM, University of Bordeaux Segolen, Bordeaux, France

Dr. Margarita Calonge Institute of Ophthalmobiology (IOBA), Universidad de Valladolid, Spain

Dr. José Becerra Ratia Dept. Biología Celular, Genética y Fisiología, Universidad de Málaga, Spain

Dr. José Carlos Rodríguez-Cabello Dept. de Física de la Materia Condensada, Universidad de Valladolid, Spain



Heart immunostainning.

Biomaterials for Regenerative Therapies

- **Prof. Kevin Healy** Biomaterials & Tissue Engineering Laboratory, University of California at Berkeley, USA
- **Prof. Jaume Veciana** NANOMOL, Institut de Ciència de Materials de Barcelona (ICMAB-CSIC), Spain
- **Dr. Diego Gutiérrez** de la Iglesia (MD) Pediatric orthopaedic surgery, San Juan de Dios Hospital, Spain
- **Prof. Wouter J.A. Dhert** & **Dr. Jos Malda** Department of Orthopaedics, University Medical Center Utrecht, The Netherlands
- **Prof. Andrés J. García**, F.B.S.E. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA
- **Prof. Alberto Muñoz** Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM, Spain
- **Dr. Luigi Ambrosio** Institute of Polymers, Composites & Biomaterials National Research Council, Naples, Italy
- **Prof. Carlos Semino** Grupo de Insuficiencia Cardíaca y Regeneración Cardíaca (ICREC), IQS School of Engineering, Universitat Ramon Llull, Spain

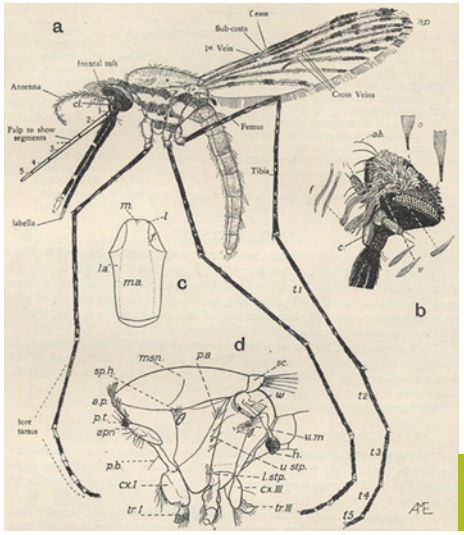
EQUIPMENT AND TECHNIQUES

- Surface characterization equipment (contact angle, Z potential, nanoindenter)
- Cell culture facilities
- Molecular Biology equipment: protein and DNA electrophoresis
- Thermocycler (PCR)
- Rapid prototyping tool (part of the Production of Biomaterials and Nanoparticles platform of the CIBER-BBN)
- Peptide synthetiser
- Combustion furnace
- Electrospinning device
- Spin-coater
- Vibrational viscosimeter

Nanomalaria (IBEC/ISGlobal joint unit)
Xavier Fernàndez-Busquets

The current activity of the Nanomalaria group is focused on the development of nanomedicine-based systems to be applied to malaria prophylaxis, diagnosis and therapy.

Malaria is arguably one of the main medical concerns worldwide because of the numbers of people affected, the severity of the disease and the complexity of the life cycle of its causative agent, the protist *Plasmodium spp*. The clinical, social and economic burden of malaria has led for the last 100 years to several waves of serious efforts to reach its control and eventual eradication, without success to this day. With the advent of nanoscience, renewed hopes have appeared of finally obtaining the long sought-after *magic bullet* against malaria in the form of a nanovector for the targeted delivery of antimalarial drugs exclusively to *Plasmodium*-infected cells. Nanotechnology can also be applied to the discovery of new antimalarials through single-molecule manipulation approaches for the identification of novel drugs targeting essential molecular components of the parasite. Finally, methods for the diagnosis of malaria can benefit from nanotools applied to the design of microfluidic-based devices for the accurate identification of the parasite's strain, its precise infective load, and the relative content of the different stages of its life cycle, whose knowledge is essential for the administration of adequate therapies. The benefits and drawbacks of these nanosystems have to be considered in different possible scenarios, including economy-related issues that are hampering the progress of nanotechnology-based medicines against malaria with the dubious argument that they are too expensive to be used in developing areas. Unfortunately, it is true that the application of nanoscience to infectious disease has been traditionally neglected, with most research resources overwhelmingly biased towards other pathologies more prominent in the developed world. Thus, extra ingenuity is demanded from us: malaria-oriented nanomedicines not only need to work spotless; they have to do so in a cost-efficient way because they will be deployed in low-income regions.



NANOpheles

Left: female Anopheles gambiae mosquito. From: John Smart, A Handbook for the Identification of Insects of Medical Importance, British Museum, London, 1948. Right: Logo of the NANOpheles project (EURONANOMED III call) coordinated by the Nanomalaria Group.

Nanomalaria (IBEC/ISGlobal joint unit)

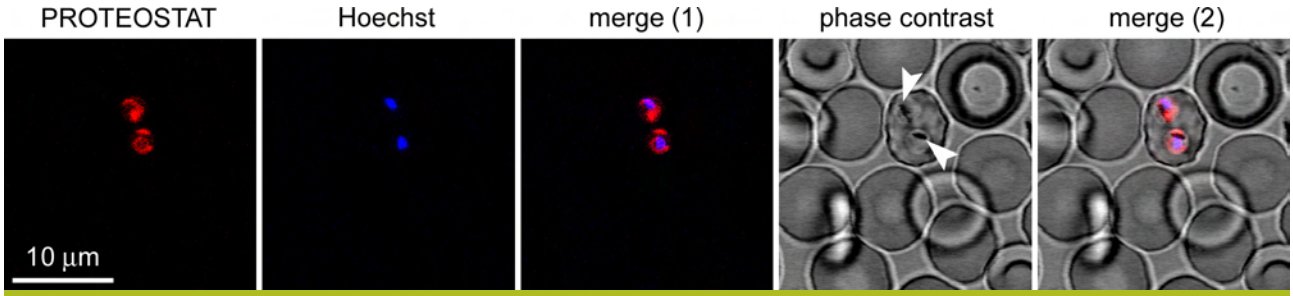
Postdocs
Yunuen Avalos
Livia Neves Borgheti

PhD students
Arnau Biosca
Inés Bouzón
Elena Lantero

Lab technician
Elisabet Martí

Visiting researcher
Carlota Roca

The driving force of the Nanomalaria group is our personal commitment to applying nanomedicine to infectious diseases of poverty through several research lines: (i) Exploration of different types of encapsulating structure (liposomes, synthetic and natural polymers), targeting molecule (protein, polysaccharide, nucleic acid aptamers), and antimalarial compound (e.g. new structures derived from marine organisms and antimicrobial peptides) for the assembly of nanovectors capable of delivering their drug cargo with complete specificity to diseased cells. (ii) Study of metabolic pathways present in *Plasmodium* but absent in humans, with the aim of identifying specific enzymes as therapeutic targets. (iii) Use of glycosaminoglycans for innovative antimalarial strategies. (iv) Design of new methods for the targeted drug delivery to *Plasmodium* stages in the mosquito vector. (v) Investigation of novel drugs against insect-borne diseases working through radically new mechanisms. (vi) Extension of our activities to new pathologies (leishmaniasis).



Fluorescence microscopy analysis of the presence of protein aggregates in P. falciparum*-infected RBCs (pRBCs). The selected field shows a single pRBC in early trophozoite stage, indicated by its characteristic nuclear Hoechst blue fluorescence among enucleated non-parasitized erythrocytes. The amyloid-specific dye PROTEOSTAT® reveals protein aggregates in the cytosol of the two parasite cells present in the pRBC. The arrowheads indicate nascent hemozoin crystals in the food vacuole of Plasmodium.*

RESEARCH PROJECTS

NANOpheles Development of nanovectors for the targeted delivery in *Anopheles* mosquitoes of agents blocking transmission of *Plasmodium* parasites (2018-2021)
Coordinator: **Xavier Fernàndez-Busquets**
Funding: EURONANOMED III. European Innovative Research & Technological Development Projects in Nanomedicine (PCIN-2017-100)

NANOMISSION Engineering of nanovectors for the delivery of antimalarial drugs to *Plasmodium* transmission forms (2015-2018).
PI: **Xavier Fernàndez-Busquets**
Funding: *Biotechnology Programme, MINECO, Spain (BIO2014-52872-R)*

Research agreement for the study of heparin-related molecules in new antimalarial strategies (2016-2018).
PI: **Xavier Fernàndez-Busquets**
Funding: *BIOIBERICA*

Group for the study of self-aggregating proteins (2017-2019).
Coordinator: **Salvador Ventura Zamora**
Consolidated Research Group certified by the Generalitat de Catalunya, Spain (2017-SGR-908)

COLLABORATIONS

Dario Anselmetti *Universität Bielefeld*, Germany. Single molecule force spectroscopy

Elisabetta Ranucci, Università degli Studi di Milano, Italy. Polyamidoamine nanoparticle synthesis

Salvador Borros, Institut Químic de Sarrià, Barcelona, Spain. Materials Chemistry

Inga Siden-Kiamos, Foundation for Research and Technology – Hellas, Heraklion, Greece. Development of the malaria parasite within the mosquito

Matthias Rottmann, Swiss Tropical and Public Health Institute, Basel, Switzerland. In vivo assays in mice of antimalarial drug nanocarriers

Paula Gomes, Universidade do Porto, Portugal. Development of new antimalarial drugs

José Antonio García Salcedo, Instituto de Parasitología y Biomedicina "López-Neyra", Consejo Superior de Investigaciones Científicas (CSIC), Granada, Spain. Synthesis of chitosan nanoparticles

Anne-Françoise Mingotaud, Université Paul Sabatier, Toulouse, France. Polymer technology

PUBLICATIONS

Quiliano, M., Pabón, A., Moles, E., Bonilla-Ramirez, L., Fabing, I., Fong, K. Y., Nieto-Aco, D. A., Wright, D. W., Pizarro, J. C., Vettorazzi, A., López de Cerain, A., Deharo, E., Fernàndez-Busquets, X., Garavito, G., Aldana, I. and Galiano, S. Structure-activity relationship of new antimalarial 1-aryl-3-susbtituted propanol derivatives: Synthesis, preliminary toxicity profiling, parasite life cycle stage studies, target exploration, and targeted delivery. European Journal of Medicinal Chemistry, 152 489-514 (2018).

Pallarès, I., de Groot, N. S., Iglesias, V., Sant'Anna, R., Biosca, A., Fernàndez-Busquets, X. and Ventura, S. Discovering putative prion-like proteins in *Plasmodium falciparum*: A computational and experimental analysis. Frontiers in Microbiology, 9 Article 1737 (2018).

Borgheti-Cardoso, L. N. and Fernàndez-Busquets, X. Turning Plasmodium survival strategies against

Nanomalaria (IBEC/ISGlobal joint unit)

Robert E. Sinden, Imperial College London, UK. *In vitro* cultures of mosquito stages of *Plasmodium*.

Fatima Nogueira, Universidade Nova de Lisboa, Portugal. Antimalarial drug assays in *Plasmodium*-infected mosquitoes and mice.

Christian Grandfils, University of Liège, Belgium. Biomaterials research.

Eva Baldrich, Hospital Universitari Vall d'Hebron, Barcelona. Malaria diagnosis.

Francisco J. Muñoz, Parc de Recerca Biomèdica de Barcelona, Spain. Amyloid diseases.

Beatriz Prieto, Universitat Rovira i Virgili, Tarragona, Spain. Development of DNA aptamers as antimalarial drugs.

Eduardo Prata Vilanova, Universidade Federal do Rio de Janeiro, Brazil. Exploration of sulfated polysaccharides of marine origin as antimalarials.

Maria Manconi, Università di Cagliari, Italy. Liposome technology.

Krijn Paaijmans, Arizona State University, Tempe, USA. Administration of drug nanocarriers to *Anopheles* mosquitoes.

Kim Williamson, Uniformed Services University of the Health Sciences, Bethesda, USA. Basic biology of bacterial, viral, and parasite diseases.

Juan José Valle-Delgado, Aalto University, Helsinki, Finland. Atomic force microscopy.

Teresa Sierra, Instituto de Nanociencia de Aragón, Zaragoza, Spain. Dendrimer technology.

Salvador Ventura, Universitat Autònoma de Barcelona, Spain. Aggregative proteins.

Ellen Faszewski, Boston University, USA. Marine sponge cell adhesion.

Jos Paulusse, University of Twente, The Netherlands. Encapsulation of peptides in tailor-made multifunctionalized nanocarriers and polyamidoamine-derived nanogels.

EQUIPMENT AND TECHNIQUES

- Zeiss Primostar microscope
- Shake 'N' Stack (Thermo Hybaid) hybridization oven
- Rotatory evaporator RS 3000-V (Selecta)
- *Plasmodium falciparum* cell cultures
- Liposome technology

itself. Future Medicinal Chemistry, 10 (19): 2245-2248 (2018).

Caddeo, C., Pucci, L., Gabriele, M., Carbone, C., Fernàndez-Busquets, X., Valenti, D., Pons, R., Vassallo, A., Fadda, A. M. and Manconi, M. Stability, biocompatibility and antioxidant activity of PEG-modified liposomes containing resveratrol. International Journal of Pharmaceutics, 538 (1): 40-47 (2018).

Caddeo, C., Manca, M. L., Peris, J. E., Usach, I., Diez-Sales, O., Matos, M., Fernàndez-Busquets, X., Fadda, A. M. and Manconi, M. Tocopherol-loaded transfersomes: In vitro antioxidant activity and efficacy in skin regeneration. International Journal of Pharmaceutics, 551 (1): 34-41 (2018).

Martí Coma-Cros, E., Biosca, A., Lantero, E., Manca, M., Caddeo, C., Gutiérrez, L., Ramírez, M., Borgheti-Cardoso, L., Manconi, M. and Fernàndez-Busquets, X. Antimalarial activity of orally administered curcumin incorporated in Eudragit®-containing liposomes. International Journal of Molecular Sciences, 19 (5): 1361 (2018).

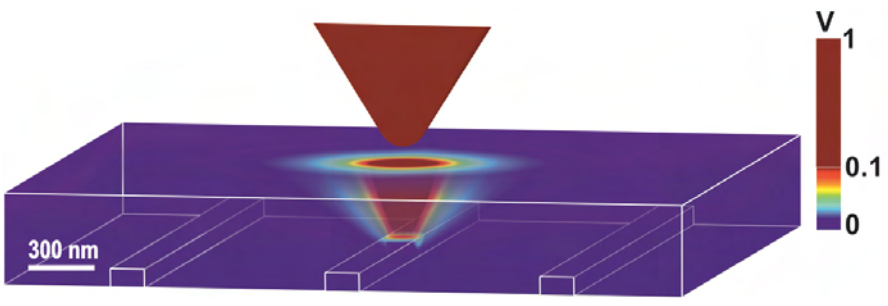
Martí Coma-Cros, E., Biosca, A., Marques, J., Carol, L., Urbán, P., Berenguer, D., Riera, M. C., Delves, M., Sinden, R. E., Valle-Delgado, J. J., Spanos, L., Siden-Kiamos, I., Pérez, P., Paaijmans, K., Rottmann, M., Manfredi, A., Ferruti, P., Ranucci, E., Fernàndez-Busquets, X., (2018). Polyamidoamine nanoparticles for the oral administration of antimalarial drugs Pharmaceutics 10, (4), 225

Nanoscale bioelectrical characterization
Gabriel Gomila

The main goal of the Nanoscale bioelectrical characterization group is to develop new experimental setups based on atomic force microscopy, and new theoretical frameworks enabling the quantification of the electrical properties of biological systems at the nanoscale (including biomembranes, single viruses, single bacteria cells and eukaryotic cells).

Our main objective is to contribute to develop new label-free biological nanoscale characterization methods and new electronic biosensors.

During 2018 the group has been involved in the investigation of the dielectric properties of water confined in nanostructures. Large-scale finite element numerical simulations of Electrostatic Force Microscopy measurements performed on nanochannels structures, contributed to reveal an anomalously low value for the dielectric constant of confined water (down to a value of ~2 as compared to a value of ~80 for bulk water). This result can have a strong impact in the understanding of the electrostatic interactions in liquid media, where such confined water can be present in most surfaces in the form of adsorbed water, including the surfaces of biological molecules. We have also completed on the dielectric properties of small-scale filamentous protein structures and applied them to the dielectric characterization of bacterial polar flagella. Results revealed a dielectric constant ~4, like that found for other macromolecular protein complexes. This result points towards a rather universal value of the dielectric constant of protein structures. We have also carried theoretical and experimental studies on the subsurface capabilities of Electrostatic Force Microscopy and the potential development of a nanotomographic technique based on it. On the other side, we continued in advancing the theoretical understanding of electrostatic force microscopy in liquid media and on its application to a variety of biological systems ranging from self-assembled monolayers and lipid bilayers to cells. During this year, we also completed our study on the electrogenic properties of Shewanella Oneidensis and identified some of the key proteins involved in the extracellular electron exchange with solid materials. We also worked on the use of organic field effect transistors for the extracellular recording of cell membrane action potentials in cardiomyocytes, obtaining results for practical applications.



Voltage distribution numerically calculated for a nanochannel-electrostatic force microscope tip structure. The numerical calculations have been used to quantify the electrostatic force acting on the tip as a function of the thickness of the nanochannels containing water. These calculations allowed demonstrating an anomalously low dielectric constant of water confined in nanochannels. The height of the channels varied from 1 nm to 200 nm and they are buried below a layer 50 nm thick.

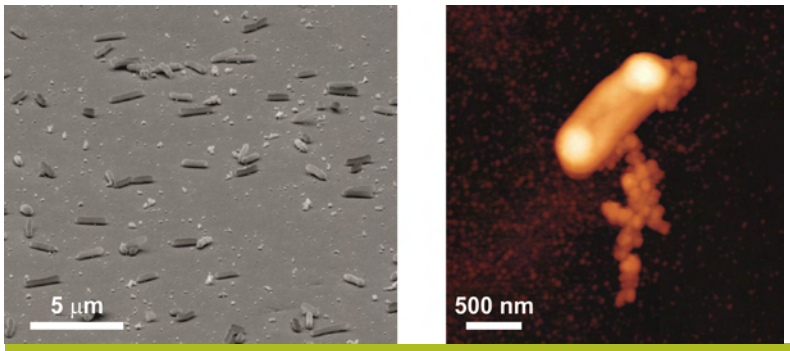
Nanoscale bioelectrical characterization

Postdocs
Ricardo Hidalgo
Lázaro René Izquierdo
Adrica Kyndiah

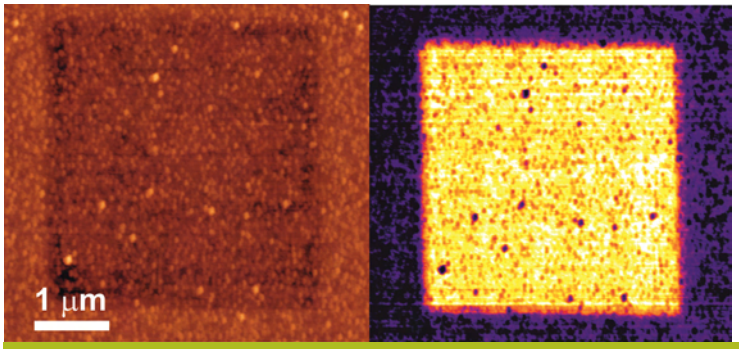
PhD students
Harishankar Balakrishnan
Martí Checa
Martina Di Muzio
Helena Lozano
Oscar Nieves

Senior technician
Rubén Millán

Visiting researcher
Maria Elena Piersimoni



(Left) Scanning Electron Microscopy image of Shewanella Oneidensis bacterial cells on a carbon substrate of an electrochemical cell. The body of the bacterial cell is known to be able to exchange electrons extracellularly with solid surfaces. We have investigated this property from macroscale electrochemical cyclic voltammetry experiments. (Right) Atomic Force Microscopy image of a Shewanella Oneidensis bacterial cell in air. The bacterial cell shows a membrane extension with globular structure, whose diameter is ~50 nm. The bacterial extensions are believed to posses also the property of exchanging electrons with solid supports and transporting electrons over long distances. We are currently investigating these properties with the use of electric scanning probe microscopy techniques (samples prepared by the group of Eduard Torrents, IBEC).



(Left) AFM Topographic and (Right) EFM dielectric images of a gold pellet 60 nm thick buried within a silicon oxide thin layer 100 nm thick. The topographic image is almost flat (~1 nm variation) while the dielectric image shows a strong contrast. This example shows the sub-surface imaging capabilities of Electrostatic Force Microscopy as compared to conventional Atomic Force Microscopy. A theoretical nanotomographic algorithm to retrieve the structural and physical properties of the buried structure has been developed.

PUBLICATIONS

■ Fumagalli, L., Esfandiar, A., Fabregas, R., Hu, S., Ares, P., Janardanan, A., Yang, Q., Radha, B., Taniguchi, T., Watanabe, K., Gomila, G., Novoselov, K. S. and Geim, A. K. Anomalously low dielectric constant of confined water. Science, 360 (6395): 1339-1342 (2018).

■ Lozano, H., Fabregas, R., Blanco, N., Millán, R., Torrents, E., Fumagalli, L. and Gomila, G. Dielectric constant of flagellin proteins measured by scanning dielectric microscopy. Nanoscale, 10 19188-19194 (2018).

■ Dols-Perez, A., Fumagalli, L. and Gomila, G. Interdigitation in spin-coated lipid layers in air. Colloids and Surfaces B: Biointerfaces, 172 400-406 (2018).

RESEARCH PROJECTS

SPM2.0 Scanning probe microscopies for nanoscale fast, tomographic and composition imaging. (2017-2020)
Coordinator: **Gabriel Gomila** | *European H2020-MSCA-ITN project*

NANOELECTROPHYS Scanning Electric Force Microscope for Electrophysiological Recordings at the Nanoscale (2016-2019)
PI: **Gabriel Gomila** | *MINECO (TEC2016-79156-P)*

BIOWIRESENSE Universal platform for biomarker detection based on conducting bacterial nanowires (2017-2019) PI: **Gabriel Gomila** | *MINECO (TEC2015-72751-EXP)*

ICREA Academia Award (2015-2019)
PI: **Gabriel Gomila** | *Catalan Institution for Research and Advanced Studies (ICREA) / Generalitat de Catalunya*

COLLABORATIONS

Dr. Laura Fumagalli, University of Manchester, United Kingdom

Dr. Ferry Kienberger, Keysight Technologies, Austria

Dr. Marta Mas-Torrens, Institute of Materials Sciences of Barcelona (ICMAB-CSIC), Spain

Dr. Moh El-Naggar, University of Southern California, USA

Dr. Buz Barstow, Cornell University, USA

Dr. Fabio Biscarini, Universita di Modena e Regio Emilia, Italy

Dr. Limin Ying, Imperial College of London, United Kingdom

Dr. Jordi Borrell, University of Barcelona, Spain

Dr. Antonio Juárez, University of Barcelona, Spain

SCIENTIFIC EQUIPMENT AND TECHNIQUES

Cypher Atomic Force Microscope (Asylum Research)

Nanowizard 4 Bio-Atomic Force Microscope (JPK)

Cervantes Atomic Force Microscope (Nanotec Electronica)

Easy Scan 2 Atomic Force Microscope (Nanosurf)

AxioImager A1m Reflection Optical Microscope (Zeiss) equipped with a AxioCam ERc5s (Zeiss)

CompactStat portable electrochemical interface and impedance analyzer (Ivium Technologies)

Palmsens 4, 8 channel Potentiostat (Palmens)

2 eLockIn204 4-phase Lock-In amplifiers (Anfatec)

Keithley 6430 sub-femtoAmp remote sourcemeter (Keithley)

Keysight B2912A precision Source/Measure Unit, 2 channels (Keysight)

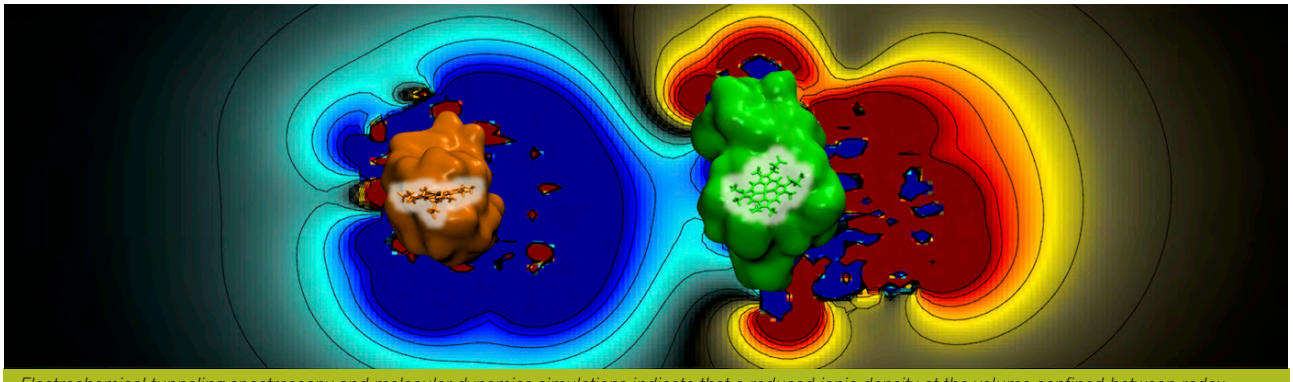
Keysight N9310A RF Signal Generator 9 kHz to 3.0 GHz (Keysight)

Nanoprobes and nanoswitches
Pau Gorostiza (ICREA Research Professor)

The group's research focuses on developing nanoscale tools to study biological systems. These tools include instrumentation based on proximity probes, such as electrochemical tunnelling microscopy and spectroscopy, that we apply to investigate electron transfer in metal oxides and individual redox proteins.

These studies are relevant to the development of biosensors and molecular electronics devices. In particular, based on our development of nanoscale field-effect transistors using individual redox protein, we have recently published a method to measure conductance switching in single redox proteins "wired" between two electrodes.

Another set of nanotools that we are developing is based on molecular actuators that can be switched with light, such as azobenzene, which can be chemically attached to biomolecules in order to optically control their activity. We have demonstrated for the first time two-photon stimulation of neurons and astrocytes with azobenzene-based photoswitches. We have also developed several bioactive compounds that have been engineered to be regulated by light. These "optopharmacological" compounds include peptide inhibitors of protein-protein interactions involved in clathrin-mediated endocytosis, and two ligands of G protein-coupled receptors (adenosine and metabotropic glutamate receptors), which are important therapeutic targets.



Electrochemical tunneling spectroscopy and molecular dynamics simulations indicate that a reduced ionic density at the volume confined between redox protein partners hCc (left, orange) and pCc1 (right, green) causes an extended electric field (equipotential lines shown in the background) that allows long distance charge transport between them. Heme groups are highlighted in each protein (Lagunas et al., 2018). Image credit: Alba Nin-Hill.

Postdocs
Marta Pozuelo
Núria Camarero
Rossella Castagna
Carlo Matera

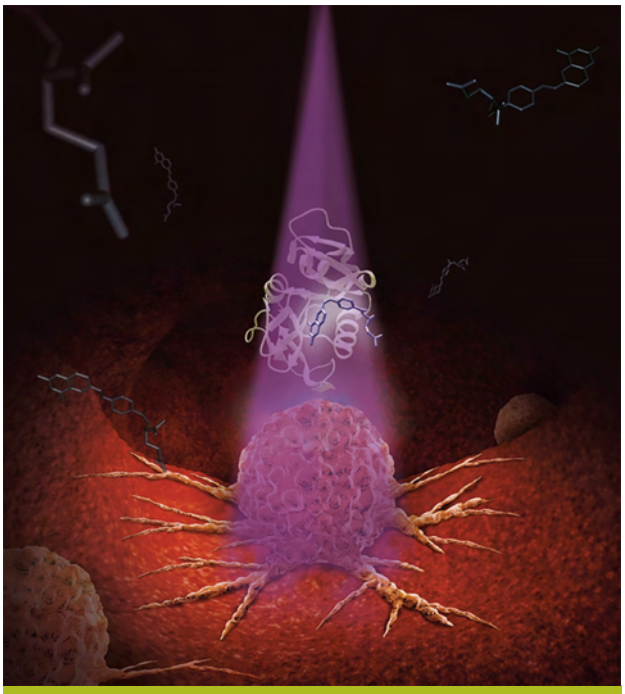
PhD students
Alejandro Martín
Aida Garrido
Alexandre Gomila
Hyojung Lee
Manuel López
Davia Prischich
Fabio Riefolo
Rosalba Sortino

Senior researchers
Marina Inés Giannotti
Ismael Díez
Mireia Oliva

Masters student
Adam Ali Dahbi Skali

Undergraduates
Cristian Ramos

Visiting researchers
Mariana Köber
Pamina Winkler



Rational structural modifications of the chemotherapy agent methotrexate enabled control of cytotoxic efficacy with light. In vitro and in vivo experiments showed that the new compound, named phototrexate, behaves as a potent antifolate in its photoactivated configuration, and that it is nearly inactive in its thermodynamically stable state. The insights provided by this work open up new possibilities for developing innovative agents for light-controlled precision chemotherapy. (Matera et al., 2018). Image credit: Carlo Matera & Grafino.it.

FILLED PATENTS

Patent Number: EP17382894.8. Patent in the field of photoactivated drugs
Assignees: IBEC, Universitat de Barcelona, ICREA, CIBER
Authors: **Pau Gorostiza**, **Concepció Soler**, **Carlo Matera**, **Núria Camarero**, **Michela Libergoli**, **Alexandre Gomila**.

RESEARCH PROJECTS

NANOPROSTHETICS Prótesis moleculares para restablecer la visiónbasadas en fotoconmutadores covalentes dirigidos (2016-2019)
PI: **Pau Gorostiza**
MINECO, Retos investigación: Proyectos I+D

MODULIGHTOR Moduladores fotoconmutables sintéticos para manipular remotamente proteínas endógenas: fotocontrol in vivo de canales iónicos pentaméricos (2015-2018)
PI: **Pau Gorostiza**
MINECO Nacional /Acciones de Programación Conjunta Internacional

PUBLICATIONS

Matera, C., Gomila-Juaneda, A., Camarero, N., Libergoli, M., Soler, C. and Gorostiza, P. A photoswitchable antimetabolite for targeted photoactivated chemotherapy. Journal of the American Chemical Society, 140 (46): 15764-15773 (2018).

Lagunas, A., Guerra-Castellano, A., Nin-Hill, A., Díaz-Moreno, I., De la Rosa, M. A., Samitier, J., Rovira, C. and Gorostiza, P. Long distance electron transfer through the aqueous solution between redox partner proteins. Nature Communications, 9 (1): 5157 (2018).

Gumí-Audenis, B., Illa-Tuset, S., Grimaldi, N., Pasquina-Lemonche, L., Ferrer-Tasies, L., Sanz, F., Veciana, J., Ratera, I., Faraudo, J., Ventosa, N. and Giannotti, M. I. Insights into the structure and nanomechanics of a quatsome membrane by force spectroscopy measurements and molecular simulations. Nanoscale, 10 (48): 23001-23011 (2018).

Inhibición fotoselectiva de interacciones proteína-proteína para el estudio de redes interactómicas y el desarrollo de nuevas terapias (2015-2018)
PI: **Pau Gorostiza**
Fundación Ramon Areces

Fotoconmutadores covalentes para el control remoto de receptores endógenos (2017-2019)
PI: **Pau Gorostiza**
Convocatoria de Ayudas a la Investigación FUNDALUCE

WaveScalES Human Brain Project Specific Grant Agreement 1 (2016-2018)
PI: **Pau Gorostiza**
European Commission, FET FLAGSHIPS, Tackling grand interdisciplinary science and technology challenges

nanoET-leukemia Nanoconductance of electron transfer proteins of the respiratory chain. Direct measurement at the single molecular level and therapeutic regulation in cancer stem cells (2015-2018)
PIs: **Anna Lagunas** (page 68) / **Marina Inés Giannotti**
MINECO, Proyectos RETOS 2015 / CIBER

Q-SPET Quantum-controlled Single Protein Electron Transport
PI: **Pau Gorostiza**
BIST-Barcelona Institute of Science and Technology BIST Ignite Program

Human Brain Project Specific Grant Agreement 2
PI: **Pau Gorostiza**
European Commission FET FLAGSHIPS/785907

FSGR Grups de recerca consolidats (2017-2019)
PI: **Pau Gorostiza**
AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1442

COLLABORATIONS

Prof. Amadeu Llebaria, Institut de Química Avançada de Catalunya (IQAC-CSIC), Spain

Prof. Ernest Giralt, Dept. de Química Orgànica, Universitat de Barcelona, Spain

Dr. Piotr Bregestovski, Institut de Neurobiologie de la Mediterraneé (INMED), Marseille, France

Dr. Mireia Oliva, Dept. de Farmàcia i Tecnologia Farmacèutica, Universitat de Barcelona, Spain

Dr. Artur Llobet, Dept. Patología y Terapéutica Experimental, Universitat de Barcelona, Spain

Dr. Joan Torrent, Escola Universitària d'Òptica i Optometria de Terrassa, Spain

Dr. Jordi Hernando, Universitat Autònoma de Barcelona, Spain

Prof. Carme Rovira, ICREA & Universitat de Barcelona, Spain

Gumi-Audenis, B., Costa, L., Redondo-Morata, L., Milhiet, P.-E., Sanz, F., Felici, R., Giannotti, M. I. and Carla, F. In-plane molecular organization of hydrated single lipid bilayers: DPPC:cholesterol. Nanoscale, 10 87-92 (2018).

Gumí-Audenis, B., Costa, L., Ferrer-Tasies, L., Ratera, I., Ventosa, N., Sanz, F. and Giannotti, M. I. Pulling lipid tubes from supported bilayers unveils the underlying substrate contribution to the membrane mechanics. Nanoscale, 10 14763-14770 (2018).

Crespo-Villanueva, A., Gumí-Audenis, B., Sanz, F., Artzner, F., Mériadec, C., Rousseau, F., Lopez, C., Giannotti, M. I. and Guyomarc'h, F. Casein interaction with lipid membranes: Are the phase state or charge density of the phospholipids affecting protein adsorption? Biochimica et Biophysica Acta (BBA) - Biomembranes, 1860 (12): 2588-2598 (2018).

Barón-Miranda, J. A., Calzadilla, O., San-Juan-Hernández, S., Diez-Perez, I., Díaz, J., Sanz, F., Chále-Lara, F. F., Espinosa, F. J. and Caballero-Briones,

- **Prof. Josep Samitier,** Institute for Bioengineering of Catalonia (IBEC) & Universitat de Barcelona (page 61)
- **Prof. Mavi Sánchez-Vives,** ICREA & IDIBAPS
- **Dr. Concepció Rovira,** Universitat de Barcelona, Spain
- **Prof. Burkhard König,** Univ Regensburg
- **Prof. Michael Decker,** Univ Würzburg

EQUIPMENT AND TECHNIQUES

- iMic molecular imaging system
- Electrochemical scanning tunnelling microscope (STM) for molecular imaging
- Asylum Research Molecular Force Probe
- Multimode SPM Nanoscope III (SCT-UB)
- Autolab potentiostat
- Patch clamp setup with Heka EPC10 amplifier
- Molecular Imaging Electrochemical STM

F. Influence of texture on the electrical properties of Al-doped ZnO films prepared by ultrasonic spray pyrolysis. Journal of Materials Science: Materials in Electronics, 29 (3): 2016-2025 (2018).

Casanellas, I., Lagunas, A., Tsintzou, I., Vida, Y., Collado, D., Pérez-Inestrosa, E., Rodríguez-Pereira, C., Magalhaes, J., Gorostiza, P., Andrades, J. A., Becerra, J. and Samitier, J. Dendrimer-based uneven nanopatterns to locally control surface adhesiveness: A method to direct chondrogenic differentiation. Journal of Visualized Experiments, Bioengineering (131): e56347 (2018).

Sebastian, P., Giannotti, M. I., Gómez, E., Feliu, J. M., (2018). Surface sensitive nickel electrodeposition in deep eutectic solvent. ACS Applied Energy Materials , 1, (3), 1016-1028

Bregestovski, Piotr, Maleeva, Galyna, Gorostiza, Pau, (2018). Light-induced regulation of ligand-gated channel activity British Journal of Pharmacology, 175, (11), 1892-1902

Biomedical signal processing and interpretation
Raimon Jané

The group's research addresses the design and development of advanced signal processing techniques and the interpretation of biomedical signals to improve non-invasive monitoring, diagnosis, disease prevention and pathology treatment.

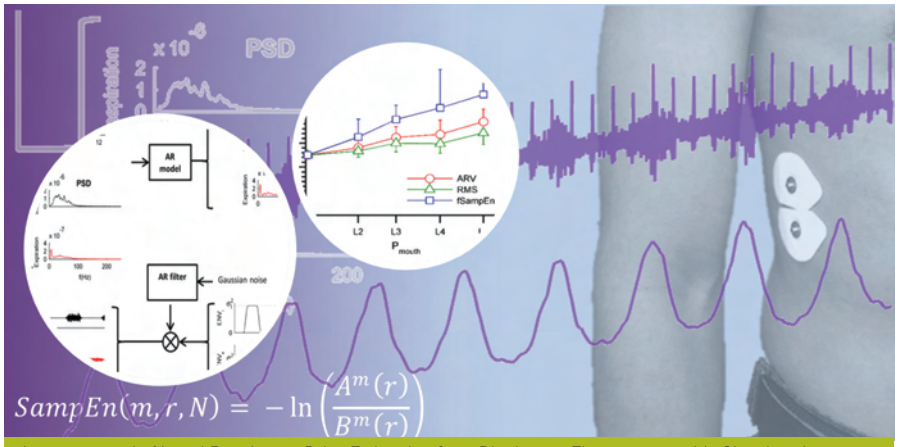
Our main objective is to improve diagnosis capability through the characterization of physiological phenomena and to enhance early detection of major cardiac and respiratory diseases and sleep disorders. We propose and design new signal processing algorithms and develop new biosignal databases, with the collaboration of our hospital partners. To validate the clinical information of new surface signals, we have developed specific invasive/non-invasive protocols and animal models. The group focuses its research in a translational way to promote the transfer of our scientific and technological contributions. Currently, our prototypes are used in hospitals for research purposes and for future industrial developments.

HIGHLIGHTS IN 2018

Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease

- Novel non-invasive measurements of neural inspiratory drive and time from invasive and noninvasive recordings of respiratory activity (Scientific Reports 2018, 8:16921; IEEE Journal Biomed Health Informatics 2018; IEEE-EMBC 2018: 3342-3345)

- Evaluation of a wearable device to determine physiological parameters from surface diaphragm electromyography (IEEE Journal Biomed Health Informatics 2018) acquired by concentric ring electrodes (IEEE-EMBC 2018: 3350-3353)



Improvement in Neural Respiratory Drive Estimation from Diaphragm Electromyographic Signals using Sample Entropy of non-invasive EMG signals (Estrada et al., 2016, IEEE Journal of Biomedical and Health Informatics).

Senior researchers
Beatriz Giraldo
Jordi Solà
Abel Torres
José Antonio Fiz

Postdocs
Manuel Lozano-Garcia
Luis Estrada
Mireia Calvo
Clare Davidson
Daniel Romero
Leonardo Sarlabous

PhD students
Javier Rodríguez
Dolores Blanco
Yolanda Castillo
Ignasi Ferrer

Masters student
Jasna Nuhic

Characterization of the microvascular cerebral blood flow response to obstructive apneic events (Neurophotonics 2018, 5: 045003) with the ICFO and the Hospital de Sant Pau.

Improvement of a front-end step for a wearable device for biosignals recording for COPD and OSA patients (IEEE Transactions on Biomedical Circuits and Systems 2018, 12: 774 – 783) with the imec, Eindhoven (NL).

Cardiac and cardiorespiratory diseases

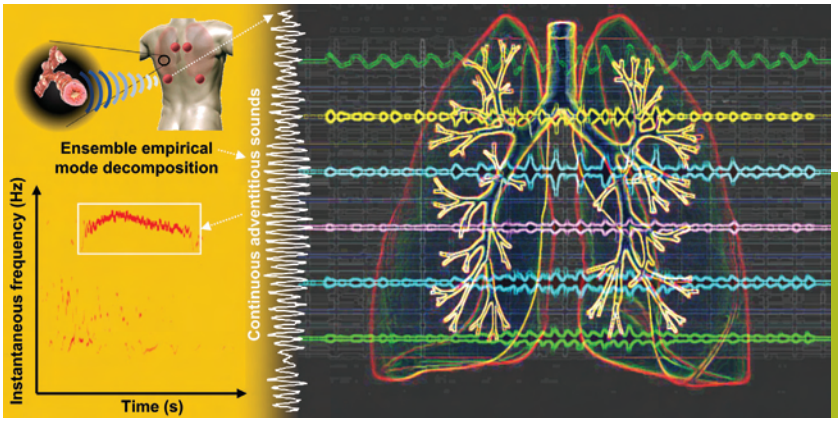
Novel eingvalue-based method for time delay estimation of respiratory signals in patients with chronic heart failure (Digital Signal Processing 2018, 75: 107-119), with Lund University, Sweden, and University of Zaragoza.

Cardirespiratory phase synchronization during mental stimuli in healthy subjects (IEEE-EMBC 2018: 5298-5301)

Estimation of sinus arrhythmia to classify ischemic cardiomyopathy (IEEE-EMBC 2018, 4860-4863) and artifact reconstruction of blood pressure signals (IEEE-EMBC 2018, 4864-4867)

Neurorehabilitation

Characterization of upper limb muscle's EMG activity during reaching and grasping (NeuroRehabilitation-ICNR 2018)



Novel method for differentiating normal from adventitious respiratory sounds (RS) to improve the diagnosis of pulmonary diseases. Particularly, continuous adventitious sounds (CAS) are of clinical interest because they reflect the severity of certain diseases. The new method is based on the multi-scale analysis of instantaneous frequency (IF) and envelope (IE) calculated after ensemble empirical mode decomposition (EEMD) of respiratory sounds. (Lozano et al., 2016, IEEE Journal of Biomedical and Health Informatics).

PUBLICATIONS

Peyman, Z., Clara, G.-P., Igor, B., Ana, F., Gianluca, C., Pau, B., Isabel, S., Anna, M., Jordi, S.-S., Beatriz, F. G.-G., Turgut, D. and Mercedes, M. Characterization of the microvascular cerebral blood flow response to obstructive apneic events during night sleep. Neurophotonics, 5 (4): 045003 (2018).

Lozano-García, M., Sarlabous, L., Moxham, J., Rafferty, G. F., Torres, A., Jané, R. and Jolley, C. J. Surface mechanomyography and electromyography provide non-invasive indices of inspiratory muscle force and activation in healthy subjects. Scientific Reports, 8 (1): 16921 (2018).

Estrada, L., Torres, A., Sarlabous, L. and Jané, R. Onset and offset estimation of the neural inspiratory time in surface diaphragm electromyography: A pilot study in healthy subjects. IEEE Journal of Biomedical and Health Informatics, 22 (1): 67-76 (2018).

Biomedical signal processing and interpretation

RESEARCH PROJECTS

M-Bio4Health Multimodal physiological biomarkers for non-invasive monitoring and home healthcare of COPD patients with comorbidities (2016-2019)
PI: **Raimon Jané**
MINECO, Retos investigación: Proyectos I+D

Non-invasive multimodal physiological biomarkers for monitoring COPD patients with comorbidities (2017-2019)
PI: **Raimon Jané**
With King's College London, funded by the European Respiratory Society (ERS-LTRF 2017)

COLLABORATIONS

Dr. J. Mark Ansermino, Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada

Prof. Antonio Bayes Genis, Grup ICREC, Servei Cardiología Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

Dr. Salvador Benito, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Prof. Dr. Konrad Bloch, Pulmonary Division, University of Zurich, Switzerland

Prof. Armin Bolz, Institute of Biomedical Engineering, University of Karlsruhe, Germany

Prof. Manuel Doblaré, Grupo de Mecánica Estructural y Modelado de Materiales, Universidad de Zaragoza, Spain

Prof. Guy Dumont, Department of Electrical and Computer Engineering, University of British Columbia, Vancouver, Canada

Prof. Ramon Farré, Unitat de Biofísica i Bioenginyeria, Facultat de Medicina, Barcelona, Spain

Dr. Javier García-Casado, Instituto Interuniversitario de Investigación en Bioingeniería y Tecnología Orientada al Ser Humano, Universidad Politécnica de Valencia, Spain

Dr. Joaquim Gea, Servei Pneumologia, Hospital del Mar-IMIM, Barcelona, Spain

Dr. Alfredo Hernández, Laboratoire Trataiment du Signal et de l'Image, Université de Rennes 1, Instituto Francés de Salud (INSERM), France

Dr. Eric Laciar, Departamento de Electrónica y Automática, Universidad Nacional de San Juan, Argentina

Prof. Pablo Laguna, Instituto de Investigación de Aragón (I3A), Universidad de Zaragoza, Spain

Dr. Barry Mersky, Audiodontics, LLC, Bethesda, Maryland, USA

Laguna, P., Garde, A., Giraldo, B. F., Meste, O., Jané, R. and Sörnmo, L. Eigenvalue-based time delay estimation of repetitive biomedical signals. Digital Signal Processing, 75 107-119 (2018).

Conference Papers

Rodríguez-Cañón, M., Delgado, I., Jané, R. and García-Alías, G. Temporal categorization of upper limb muscle's EMG activity during reaching and grasping. 4th International Conference on NeuroRehabilitation (ICNR2018). Pisa, Italy (2018). Published by Springer, Cham (2018/10/16).

Rafols-De-Urquia, M., Estevez-Piorno, J., Estrada, L., Garcia-Casado, J., Prats-Boluda, G., Sarlabous, L., Jane, R. and Torres, A. Assessment of respiratory muscle activity with surface electromyographic signals acquired by concentric ring electrodes. 40th Annual International Conference of the IEEE. Honolulu, USA (2018). Published by IEEE (2018/10/29).

Lozano-Garcia, M., Sarlabous, L., Moxham, J., Rafferty, G. F., Torres, A., Jolley, C. J. and Jane, R. Assessment of inspiratory muscle activation using surface diaphragm

- **Prof. Dr. Thomas Penzel,** Interdisciplinary Sleep Center, Charité University Hospital, Berlin, Germany
- **Dr. Josep Morera Prat,** Servicio de Neumología, Hospital Germans Trias i Pujol, Badalona, Spain
- **Prof. Winfried J. Randerath,** Institut für Pneumologie, Klinik Bethanien, Solingen, Germany
- **Dr. Juan Ruiz,** Servei de Pneumología de l'Hospital Germans Trias i Pujol de Badalona
- **Dr. Matthias,** Schwaibold MCC-Med GmbH & Co. KG, Karlsruhe, Germany
- **Prof. Dr. Lotfi Senhadji,** Laboratoire Traitement du Signal et de l'Image (LTSI), Université de Rennes 1, Institut National de la Santé et de la Recherche Médicale (INSERM), France
- **Prof. Leif Sörnmo,** Signal processing group, Lund University, Sweden
- **Prof. Dr. Jaume Veciana,** Grupo de Nanociencia Molecular y Materiales Orgánicos del Instituto de Ciencia de Materiales de Barcelona (NANOMOLCSIC), Barcelona
- **Prof. Andreas Voss,** University of Applied Sciences, Jena, Germany
- **Dr. Pierluigi Casale,** Laboratory for advanced research in microelectronics (IMEC), Eindhoven, The Netherlands
- **Dr. Francky Catthoor,** Laboratory for advanced research in microelectronics (IMEC), Leuven, Belgium
- **Dr. Miquel Domenech,** Dep. of Social Psychology, Universitat Autònoma de Barcelona
- **Dr. Caroline Jolley / Prof. John Moxham,** King's College London, UK
- **Prof. Richard Reilly,** Trinity College Dublin, Ireland

EQUIPMENT AND TECHNIQUES

- Research laboratory with full equipment for acquisition and processing of biomedical signal to test new sensors and to define clinical protocols (preliminary tests and control subjects)
- Non-invasive Vital Signs Monitor for small lab animals (mice and rats) (Mouse-Ox Plus)
- BIOPAC system for multichannel cardiac and respiratory biomedical signal acquisition
- Databases of biomedical signals from hospitals and animal laboratories
- Snoring analyzer equipment (SNORYZER)
- Sensors, electrodes and microphones to obtain cardiac, respiratory, neural, muscular and sleep biomedical signals

mechanomyography and crural diaphragm electromyography. 40th Annual International Conference of the IEEE. Honolulu, USA (2018). Published by IEEE (2018/10/29).

Giraldo, B. F., Pericàs, M. F., Schröeder, R. and Voss, A. Respiratory sinus arrhythmia quantified with linear and non-linear techniques to classify dilated and ischemic cardiomyopathy. 40th Annual International Conference of the IEEE. Honolulu, USA (2018). Published by IEEE (2018/10/29).

Rodríguez, J. and Giraldo, B. F. A novel artifact reconstruction method applied to blood pressure signals. 40th Annual International Conference of the IEEE. Honolulu, USA (2018). Published by IEEE (2018/10/29).

Solá-Soler, J., Cuadros, A. and Giraldo, B. F. Cardiorespiratory phase synchronization increases during certain mental stimuli in healthy subjects. 40th Annual International Conference of the IEEE. Honolulu, USA (2018). Published by IEEE (2018/10/29).

2018 Research and Services

Biomedical signal processing and interpretation

- Polisomnographic equipment available in the Sleep Laboratory of collaborator hospital
- Finometer beat to beat arterial blood pressure and haemodynamic monitor equipment
- Computing server for high performance biomedical signals
- Threshold™ IMT (Inspiratory Muscle Trainner) for respiratory muscle training (Phillips™)
- Robust wearable wireless sensor device Shimmer3 (Shimmer Research Ltd., Dublin, Ireland).
- PowerBreath KH1 and Breath Link software (PowerBreath®).
- Smartphones Samsung™ Galaxy for mHealth applications
- MicroUSB-wired pulse oximeter (Kenek Edge, LionsGate Technologies Inc.).
- BIOPAC high-sensitivity tri-axial accelerometers (MMG) and conventional and ring electrodes.

Signal and information processing for sensing systems
Santiago Marco

Current smart instrumentation using multi-sensors and/or spectrometers provides a wealth of data that requires sophisticated signal and data processing approaches to extract the hidden information.

In this context, we are interested in intelligent chemical instruments for the detection of volatile compounds and smells.

These systems can be based on an array of nonspecific chemical sensors with a pattern recognition engine, taking inspiration from the olfactory system. Some spectrometries, e.g. Ion Mobility Spectrometry, are capable of very fast analysis with good detection limits but poor selectivity. These technologies have been proposed for the fast determination of the volatolome (volatile fraction of the metabolome), instead of the reference technique of gas chromatography – mass spectrometry.

Our group develops algorithmic solutions for the automatic processing of Gas Sensor Array, Ion Mobility Spectrometry (IMS) and Gas Chromatography – Mass Spectrometry (GC-MS) data for metabolomics and food samples.

Fast Photo-Ionization Detector to study turbulent plume dynamics and their impact in olfactory navigation.

Our Research in 2018 included

1. Development of an analytical method based on Thermal Desorption Ion Mobility Spectrometry for the fast detection of cannabinoids in collaboration with the University of Córdoba, Spain

2. The identification Volatile Fingerprints to evaluate the quality of Bitter Orange Essential Oils using Machine Learning

3. We have studied the impact of low power operation modes in the performance of Metal Oxide Sensors

4. We are developing algorithms for the analysis of mass spectrometry images for the study of heterogeneity in colorectal cancer tissues

5. We are developing analytical methods for the study of the majoritary compounds in human flatus in collaboration with Dr. F. Aspiroz (Hospital Vall d'Hebron)

6. We have proposed methods to estimate the limit of detection in non-linear chemical sensors using univariate and multivariate calibration models

7. We have proposed methods to find universal calibration models for chemical sensor arrays

8. We have studied the impact of cross-validation methods in the overoptimism of PLS-DA models applied to omics data

9. We have proposed methods to evaluate and correct the impact of instrumental shifts in GC-MS data for breath metabolomics

Signal and information processing for sensing systems

Senior researcher
Agustín Gutiérrez

Postdocs
Jordi Fonollosa
Lluís Fernández
Luciana Fontes de Oliveira
Rafael Teixera Freire
Francisco Javier Madrid
Silvia Mas

PhD student
Javier Burgués

Research assistant
Celia Mallafré

Visiting researcher
Dominique Martinez

Fast TCA detection in corks using Ion Mobility Spectrometry technology (in collaboration with 3control Industrial Automation and Vision SL).

RESEARCH PROJECTS

Development of Data Processing Algorithms for Temperature Modulated Sensors
PI: **Santiago Marco**
Industrial Project with BSH Electrodomesticos, Spain

Computational Metabolomics (2017-2019)
PI: **Santiago Marco**
Industrial Project with Nestlé Institute of Health Sciences, Switzerland

SIGVOL Mejora de la señal para instrumentación química: aplicaciones en metabolómica de volátiles y en olfacción
PI: **Santiago Marco**
MINECO Retos investigación: Proyectos I+D/TEC2014-59229-R

PUBLICATIONS

Solórzano, A., Rodríguez-Pérez, R., Padilla, M., Graunke, T., Fernandez, L., Marco, S. and Fonollosa, J. Multi-unit calibration rejects inherent device variability of chemical sensor arrays. Sensors and Actuators B: Chemical, 265 142-154 (2018).

Contreras, M. D. M., Jurado-Campos, N., Sánchez-Carnerero Callado, C., Arroyo-Manzanares, N., Fernández, L., Casano, S., Marco, S., Arce, L. and Ferreiro-Vera, C. Thermal desorption-ion mobility spectrometry: A rapid sensor for the detection of cannabinoids and discrimination of Cannabis sativa L. chemotypes. Sensors and Actuators B: Chemical, 273 1413-1424 (2018).

Burgués, J. and Marco, S. Multivariate estimation of the limit of detection by orthogonal partial least squares in temperature-modulated MOX sensors. Analytica Chimica Acta, 1019 49-64 (2018).

Burgués, J., Jiménez-Soto, J. M. and Marco, S. Estimation of the limit of detection in semiconductor gas sensors through linearized calibration models. Analytica Chimica Acta, 1013 13-25 (2018).

Fernandez, L., Yan, J., Fonollosa, J., Burgués, J., Gutierrez, A. and Marco, S. A practical method to estimate the resolving power of a chemical sensor array: Application to feature selection. Frontiers in Chemistry, 6 Article 209 (2018).

Oller-Moreno, S., Cominetti, O., Galindo, A. N., Irincheeva, I., Corthésy, J., Astrup, A., Saris, W. H. M., Hager, J., Kussmann, M. and Dayon, L. The differential plasma proteome of obese and overweight individuals undergoing a nutritional weight loss and maintenance intervention. PROTEOMICS - Clinical Applications, 12 (1): 1600150 (2018).

Rodríguez, R., Cortés, R., Verónica

COLLABORATIONS

- **Dr. Lourdes Arce**, Dept. Química Analítica, Universidad de Córdoba, Spain
- **Prof. J. W. Gardner**, Microsensors and Bioelectronics Lab, Dept. of Electric and Electronic Engineering, University of Warwick, UK
- **Prof. Achim Lilienthal**, Mobile Robotics and Olfaction Lab, University of Örebro, Sweden
- **Dr. Ivan Montoliu and Dra. Sofia Moço**, Nestlé Institute of Health Sciences, Laussane, Switzerland
- **Dr. Jordi Palacín**, Robotics Lab, Universitat de Lleida, Spain
- **Dra. Cristina Castro**, Sensors Technology, BSH-Zaragoza, Spain
- **Dr. Jens Eichman**, MINIMAX, Bad Oldesloe, Germany
- **Dr. Ulf Struckmeier**, AMS sensors, Reutlingen, Germany
- **Dr. Fernando Azpiroz**, Dept. Digestive Diseases, Vall d'Hebron, Barcelona, Spain
- **Dra. Anna de Juan**, Dept. Química Analítica i Enginyeria Química, Universitat de Barcelona, Spain
- **Dr. Oriol Sibila**, IBB Sant Pau, Asthma Group and Hospital de Sant Pau, Spain
- **Dr. Alvar Agustí**, IDIBAPS (Inflammation and repair in respiratory illnesses Group) and Hospital Clínic de Barcelona, Spain

EQUIPMENT AND TECHNIQUES

- Gas chromatograph/mass spectrometer (Thermoscientific) with robotic head-space sampler
- Gas Chromatograph/ Thermal Conductivity Detector (Thermoscientific) with robotic head-space sampler
- 2 Infusion pumps K-systems
- 6 channel vapor generator plus humidity control (Owlstone, UK)
- Ion Mobility Spectrometer: Gas Detector Array (Airsense Analytics GmbH)
- Computing and General Purpose Electronic Instrumentation
- Field Asymmetric Ion Mobility Spectrometer (Owlstone, UK)
- Corona Discharge Ion Mobility Spectrometer (3QBD, Israel)
- Ultraviolet Ion Mobility Spectrometer (Gas Dortmund, Germany)
- Fast Photo Ionization Detector (Aurora Scientific, Canada)

Guamán, A., Pardo, A., Torralba, Y., Gómez, F., Roca, J., Barberà, J. A., Cascante, M. and Marco, S. Instrumental drift removal in GC-MS data for breath analysis: the short-term and long-term temporal validation of putative biomarkers for COPD. Journal of Breath Research, 12 (3): 036007 (2018).

- Rodríguez-Pérez, R., Fernández, L. and Marco, S. Overoptimism in cross-validation when using partial least squares-discriminant analysis for omics data: a systematic study. Analytical and Bioanalytical Chemistry, 410 (23): 5981-5992 (2018).
- Taghadomi-Saberi, S., Garcia, S. M., Masoumi, A. A., Sadeghi, M. and Marco, S. Classification of bitter orange essential oils according to fruit ripening stage by untargeted chemical profiling and machine learning. Sensors, 18 (6): 1922 (2018).
- Fonollosa, J., Solórzano, A. and Marco, S. Chemical sensor systems and associated algorithms for fire detection: A review. Sensors, 18 (2): 553 (2018).
- Burgués, J. and Marco, S. Low power operation of temperature-modulated metal oxide semiconductor gas sensors. Sensors, 18 (2): 339 (2018).

Conference Papers

- Burgués, J., Hernandez, V., Lilienthal, A. J. and Marco, S. 3D Gas distribution with and without artificial airflow: An experimental study with a grid of metal oxide semiconductor gas sensors. EUROSENSORS 2018. Graz, Austria (2018). Published by MDPI (2018/11/29).

Book Chapter

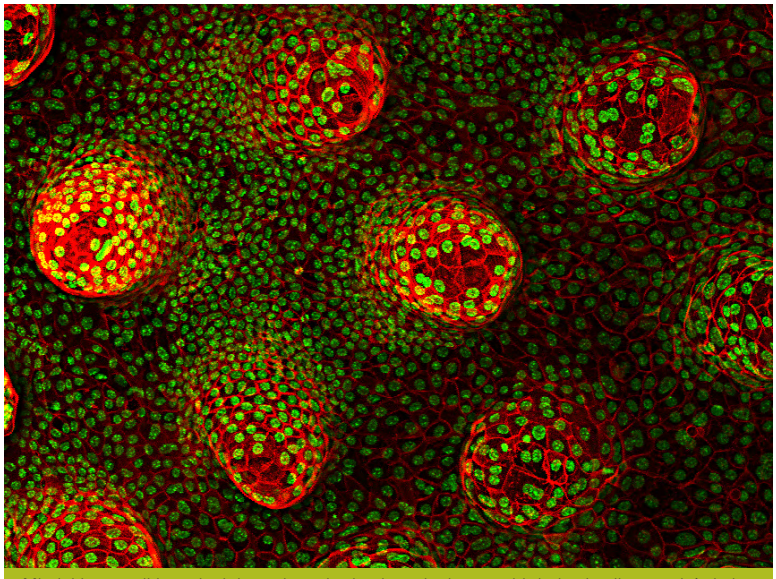
- Rodríguez-Pérez, R., Padilla, M. and Marco, S. The need of external validation for metabolomics predictive models. In: Volatile Organic Compound Analysis in Biomedical Diagnosis Applications (ed. Cumeras, R. and Correig, X.). New York, USA, Apple Academic Press. PART III: COMPUTATIONAL TOOLS: 225-252 (2018).

Biomimetic systems for cell engineering
Elena Martínez

In vitro assay platforms involving human cells are increasingly important to study tissue development, tissue regeneration, construct models of disease or develop systems for therapeutic screening that predict the human in vivo context.

The main conceptual problem of the standard in vitro cell-based assays is that they rely on two dimensional monolayer cellular cultures, which fail to replicate the complexity of living systems. There is an urgent need to create technological platforms with complex cell culture systems that mimic better the tissue-like cellular microenvironment.

We propose to combine engineering microfabrication technologies, tissue engineering concepts and recent advances in stem cell research, exploiting stem cell unique properties, to create cell culture microenvironments that will go beyond current 3D in vitro models. Resulting in vitro tissue equivalents aim at recapitulating in vivo cell functionality, cell renewal and migration, multicell-type differentiation and cell-matrix and cell-cell interactions. The cell culture platforms proposed will provide physiologically relevant and highly reproducible data, and they will be compatible with conventional cell culture assays and high-throughput testing. The new organotypic cell culture platforms will aim to advance the in vitro modelling of diseases, the preclinical screening for drug toxicity, the understanding of organ development and the regenerative medicine applications. Current main projects are: (i) to engineer and validate a complex in vitro model of small intestinal epithelium and (ii) to engineer and validate a novel in vitro model of engineered cardiac tissue.



Mimicking small intestinal tissue by culturing intestinal-organoid derived cells on poly(ethylene glycol) diacrylate (PEGDA) microstructures. Cell nuclei are stained in green and actin cytoskeleton in red.

Postdocs
Gizem Altay
María García
Núria Torras

PhD students
Aina Abad
Enara Larrañaga
Anna Vila

Masters students
Raquel Alonso

Undergraduates
Julia Kubitz

Research Assistants
Jon Zabalo

Senior postdoc
Jordi Comelles

Senior researcher
Vanesa Fernández

Senior Technician
Raquel Obregón

RESEARCH PROJECTS

INDUCT Dispositivo de multitejido intestinal para la monitorización de la comunicación entre epitelio y músculo en condiciones patológicas (2018-2021)
PI: **Elena Martínez**
MINECO

ENGUT Engineered models of intestinal epithelial tissue: assessing in vivo-like functional properties (2018)
PI: **Elena Martínez /Emilio J. Gualda**
BIST

Cardiopoesi amb biomatrius per regenerar la cicatriu post infart: From bench to bedside (first-in-man trial) (2017-2019)
PI: **Daniel Navajas** (page 48)
Pla Estratègic de Recerca i Innovació en Salut (PERIS) SLT002/16/00234

REPROMICRO Reprogramación y regeneración tisular a partir de microvesiculas derivadas de células madre de pluripotencia inducida (2017-2018)
PI: **Nuria Montserrat** (page 39)
MINECO (EXPLORA)

COMIET Engineering Complex Intestinal Epithelial Tissue Models (2015-2020)
PI: **Elena Martínez**
ERC Consolidator Grant

GLAM Glass-Laser Multiplexed Biosensor (2015-2019)
PI: **Elena Martínez**
European Commission (H2020) – PHC-10-2015

COLLABORATIONS

Prof. Ángel Raya, Center of Regenerative Medicine in Barcelona (CMRB), Barcelona, Spain

Prof. Eduard Batlle, Institut de Recerca Biomédica (IRB), Barcelona, Spain

Prof. Pablo Loza, Institut de Ciències Fotòniques (ICFO), Castelldefels, Spain

Dr. Samuel Ojosnegros, Institute for Bioengineering of Catalonia (IBEC) (page 87)

Dr. Javier Ramón, IInstitute for Bioengineering of Catalonia (IBEC) (page 51)

Dr. Elisabeth Engel, Institute for Bioengineering of Catalonia (IBEC) (page 13)

Prof. Raimon Jané, Institute for Bioengineering of Catalonia (IBEC) (page 28)

PUBLICATIONS

García-Díaz, M., Birch, D., Wan, F. and Mørck Nielsen, H. The role of mucus as an invisible cloak to transepithelial drug delivery by nanoparticles. Advanced Drug Delivery Reviews, 124 107-124 (2018).

Hortigüela, V., Larrañaga, E., Cutrale, F., Seriola', A., García-Díaz, M., Lagunas, A., Andilla, J., Loza-Alvarez, P., Samitier, J., Ojosnegros', S. and Martinez, E. Nanopatterns of surface-bound ephrinB1 produce multivalent ligand-receptor interactions that tune EphB2 receptor clustering. Nano Letters, 18 (1): 629-637 (2018).

Macedo, M. H., Araújo, F., Martínez, E., Barrias, C. and Sarmento, B. iPSC-Derived enterocyte-like cells for drug absorption and metabolism studies. Trends in Molecular Medicine, 24 (8): 696-708 (2018).

Torras, N., García-Díaz, M., Fernández-Majada, V. and Martínez, E. Mimicking epithelial tissues in three-dimensional cell culture models. Frontiers

Biomimetic systems for cell engineering

Prof. Josep Samitier, Institute for Bioengineering of Catalonia (IBEC) (page 61)

Prof. Javier Santos, Dra. Maria Vicario, VHIR, Barcelona, Spain

Dr. Bruno Sarmento, i3S - Instituto de Investigação e Inovação em Saúde, Porto, Portugal

Dr. Sonia García-Blanco, University of Twente, Enschede, The Netherlands

Dr. Fabio Variola, University of Ottawa, Ottawa, Canada

Dr. Daniel Riveline, ISIS/IGBMC, Strasbourg, France

Dr. Matthew Dalby, University of Glasgow, Glasgow, UK

Prof. Jordi Martorell, Institut de Ciències Fotòniques (ICFO), Castelldefels, Spain

Prof. José Antonio Plaza, CNM-CSIC, Barcelona, Spain

Dr. Francesc Mitjans, LEITAT, Barcelona, Spain

EQUIPMENT AND TECHNIQUES

Micro and nanofabrication techniques:
- Biomolecule gradients produced by microfluidics
- Large-area nanostructured polymer surfaces produced by diblock copolymers
- 3D microstructures on hydrogel materials
- Multistimuli mini-bioreactor for 3D cell culture

Characterization techniques:
- Surface Plasmon Resonance (SPR) measurements on polymer materials
- Atomic Force Microscope (AFM) expertise
- Optical Microscopes (white light/epifluorescence)
- Focused Ion Beam (FIB) / Scanning Electron Microscopy (SEM) of biological specimens

Equipment:
- Biological safety cabinet (class II)
- High precision syringe pumps
- Peristaltic pumps

Access to the Nanotechnology Platform (IBEC Core Facilities): equipment for hot embossing lithography, polymer processing and photolithography, chemical wet etching, e-beam evaporation and surface characterization (TOF-SIMS)

Access to the Scientific and Technological Centers (University of Barcelona): equipment for surface analysis (XPS, AFM, XRD) and microscopy techniques (SEM, TEM, confocal)

in Bioengineering and Biotechnology, 6 Article 197 (2018).

Conference Papers

de Goede, M., Dijkstra, M., Obregón, R., Martínez, E. and García-Blanco, S. M. High quality factor Al2O3 microring resonators for on-chip sensing applications. SPIE OPTO. California, USA (2018). Published by SPIE (2018/02/23).

de Goede, M., Chang, L., Dijkstra, M., Obregón, R., Ramón-Azcon, J., Martínez, E., Padilla, L., Adan, J., Mitjans, F. and García-Blanco, S. M. Al2O3 Mmicroresonators for passive and active sensing applications. Optical Sensors. Zurich, Switzerland (2018). Published by OSA - The Optical Society (2018/07/05).

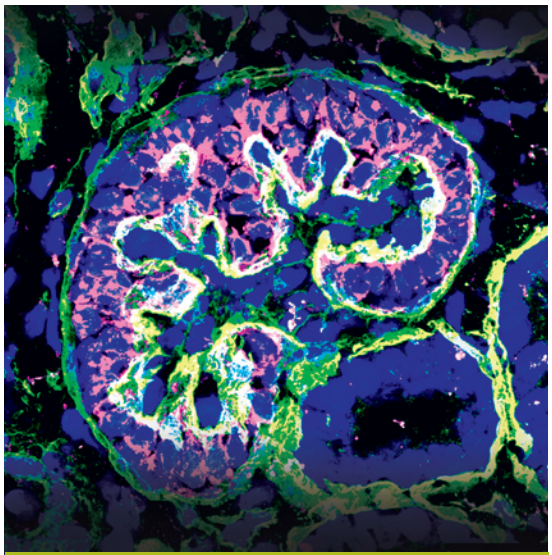
de Goede, M., Chang, L., Dijkstra, M., Obregón, R., Ramón-Azcon, J., Martínez, E., Padilla, L., Adan, J., Mitjans, F. and García-Blanco, S. M. Al2O3 Microresonator based passive and active biosensors. 20th International Conference on Transparent Optical Networks. Bucharest, Romania (2018). Published by IEEE Computer Society (2018/07/01).

Pluripotency for organ regeneration
Núria Montserrat (ICREA Research Professor)

The generation of induced pluripotent stem cells (iPSCs), especially the generation of patient-derived pluripotent stem cells suitable for disease modelling in vitro, opens the door for the potential translation of stem-cell related studies into the clinic.

Successful replacement, or augmentation, of the function of damaged cells by patient derived differentiated stem cells would provide a novel cell-based therapy for diseases. Since iPSCs resemble human embryonic stem cells (hESCs) in their ability to generate cells of three germ layers, patient-specific iPSCs offer definitive solutions for the ethical and histo-incompatibility issues related to hESCs. Indeed human iPSC (hiPSC)-based autologous transplantation is heralded as the future of regenerative medicine.

One of our aims is to generate and correct disease-specific hiPSCs for disease modelling and drug screening. The combination of gene-editing based methodologies together with the development of novel protocols for cell differentiation into relevant tissues/organs, provides a unique scenario for modelling disease progression, and the identification of molecular and cellular mechanisms leading to organ regeneration (Figure 1). In this regard we are particularly interested in generation of transgene-free and disease free patient derived hiPSCs for disease modelling and the discovery of novel therapeutic targets.



(Fig. 1) Detail of renal glomerular cells during embryonic development.

We believe that the recovery of tissue function should not be restricted to the development of cell replacement therapies. In this regard, in our laboratory we take advantage of organisms that possess the ability to regenerate such as zebrafish, in order to understand which molecular and cellular pathways lead to organ regeneration. Surprisingly, studies in neonatal mice have demonstrated that soon after birth this organism posses the capability to regenerate its heart. Taking advantage of such preliminary observations we are translating such analysis in order to understand if the mammalian neonatal kidney still posses the capability to regenerate, and more importantly, if we are able to dissect the epigenetic and cellular mechanisms leading to those responses.

Lastly, and in an effort to fully develop in vitro and ex vivo platforms for organ regeneration, in our lab we are focused in the development of reporter cell lines for different transcription factors essential for tissue-specific commitment and differentiation (i.e: renal and cardiac lineages). The possibility to combine pluripotent stem cell lines together with decellularized matrices, functionalized biomaterials and ex vivo organoids offers and unprecedented opportunity for the immediate generation of patient-specific in vitro and ex vivo platforms for disease modelling and organ regeneration (Figure 2).

Pluripotency for organ regeneration

Senior researchers
Elena Garreta
Federico González

Postdoc
Carmen Hurtado

PhD students
Andrés Marco
Patricia Katherine Prado
Idoia Lucía Selfa

Masters students
Elena Laplaza
Guillem Murciano
Giuseppe Pierpaolo

Undergraduates
Victor López

Research Assistant
Maria Gallo

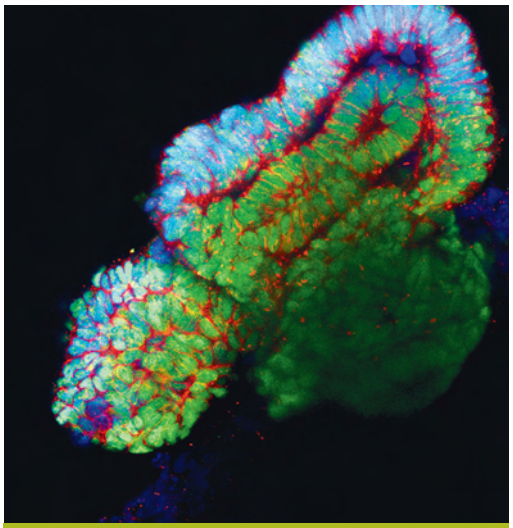
Senior technician
Carolina Tarantino

Visiting researchers
Sergi Àngel Bonilla
Blanca Molins

RESEARCH PROJECTS

How to model Diabetic Nephropathy: resetting the epigenome in experimentally-induced diabetic kidney organoids (2018-2020)
PI: **Núria Montserrat** | *Spanish Ministry of Economy and Competitiveness (Proyectos I+D+i)*

National Network in Cell Therapy (2017-2021)
PI: **Núria Montserrat** | *Institute of Health Carlos III (Thematic Networks for Cooperative Research in Health)*



(Fig. 2) Detail of glomerular structures in renal organoids from pluripotent stem cells.

Generation of Isogenic Models of Clear Cell Renal Cell Carcinoma (ccRCC) using CRISPR-engineered Kidney Organoids, for the identification of diagnostic biomarkers (2017-2020)
PI: **Núria Montserrat** | *Spanish Association Against Cancer (Lab AECC)*

Stem cells and regeneration (2017-2020)
PI: **Núria Montserrat** | *Catalan Government (Consolidated Research Groups)*

Tissue reprogramming and regeneration through microvesicles from induced pluripotent stem cells (2017-2019)
PI: **Núria Montserrat** | *Spanish Ministry of Economy and Competitiveness (Proyectos Explora)*

CHONDREG Identification of the epigenetic mechanisms preventing Chondrocyte de-differentiation: generation of novel therapeutic strategies for the treatment of cartilage chronic osteochondral lesions (2017-2019)
PI: **Núria Montserrat** | *Biomedical Research Networking Centre (Tech Transfer Program)*

How to regenerate the mammalian kidney (2015-2020)
PI: **Núria Montserrat** | *European Research Council (ERC-StG-2014)*

Ramón y Cajal Fellow (2015-2019)
PI: **Núria Montserrat** | *Spanish Ministry of Economy and Competitiveness*

PUBLICATIONS

Latorre, E., Kale, S., Casares, L., Gómez-González, M., Uroz, M., Valon, L., Nair, R. V., Garreta, E., Montserrat, N., del Campo, A., Ladoux, B., Arroyo, M. and Trepat, X. Active superelasticity in three-dimensional epithelia of controlled shape. Nature, 563 (7730): 203-208 (2018).

Hernandez-Benitez, R., Llanos Martinez-Martinez, M., Lajara, J., Magistretti, P., Montserrat, N. and Izpisua Belmonte, J. C. At the heart of genome editing and cardiovascular diseases. Circulation Research, 123 (2): 221-223 (2018).

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COLLABORATIONS

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- **Dr. Pedro Guillén**, Director Clínica Cemtro, Madrid, Spain
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- **Joaquin Gutiérrez Fruitós**, University of Barcelona, Spain
- **Dr. Cristina Eguizabal Argaiz**, Centro Vasco de Transfusión y Tejidos Humanos (CVTTH), Bizkaia, Spain

EQUIPMENT AND TECHNIQUES

- Real Time QuantStudio 5
- SimpliAmp thermocycler
- Eppendorf 5415D centrifuge
- Allegra X-15 R centrifuge
- Gyrozen 1248 centrifuge
- BioUltra 6 Telstar culture Hood 2x
- AH-100 Telstar primary culture Hood
- Binder CB 60 incubators 2x
- Controltecnica ASTEC SCA 165 incubator
- Controltecnica ZC 180 incubator
- Bioruptor Pico sonicator
- Thermomixer C thermal block
- Leica DMS1000 and DMIL Led microscopes
- Leica DMi1 microscope
- Leica MZ 10F magnifying glass
- Safe Imager 2.0 transilluminator

Laufer, N., Kochman, R., Eldar-Geva, T., Lunenfeld, B., Ezcurra, D., D'Hooghe, T., Fauser, B. C. J. M., Tarlatzis, B. C., Meldrum, D. R., Casper, R. F., Fatemi, H. M., Devroey, P., Galliano, D., Wikland, M., Sigman, M., Schoor, R. A., Goldstein, M., Lipshultz, L. I., Schlegel, P. N., Hussein, A., Oates, R. D., Brannigan, R. E., Ross, H. E., Pennings, G., Klock, S. C., Brown, S., Van Steirteghem, A., Rebar, R. W. and LaBarbera, A. R. Forty years of IVF. Fertility and Sterility, 110 (2): 185-324 (2018).

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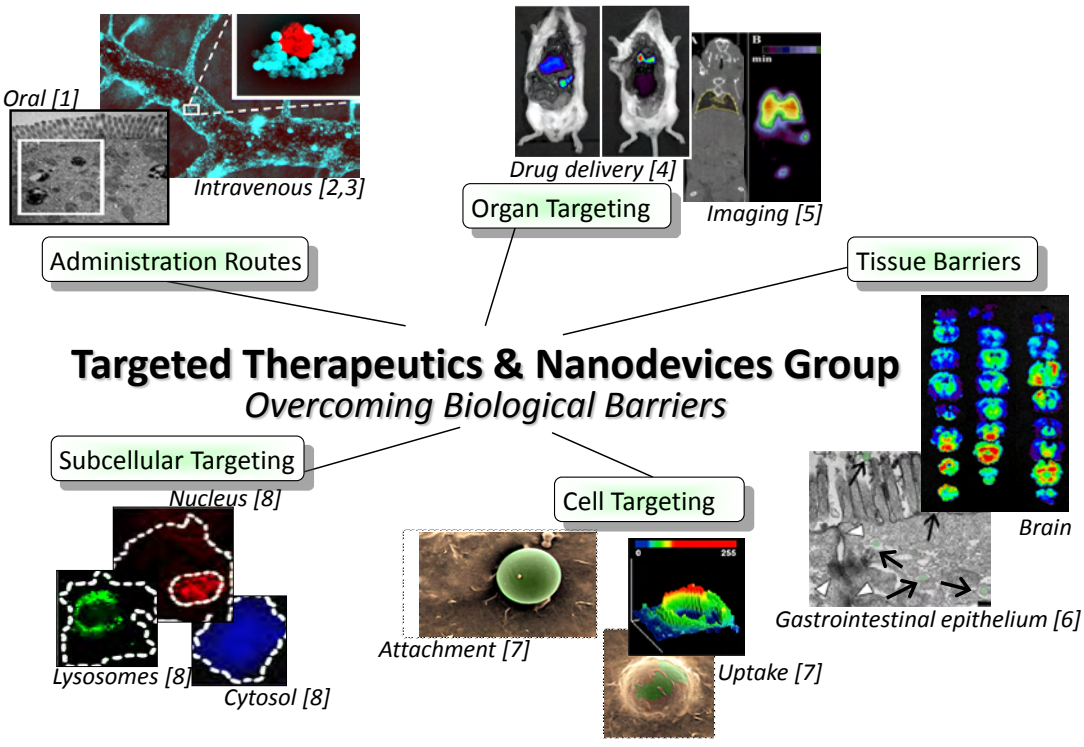
Targeted therapeutics and nanodevices
Silvia Muro (ICREA Research Professor)

Our research sits at the interface between molecular-cellular biology and nanotechnology-drug delivery. We study the biological mechanisms ruling how our cells and tissues transport cargoes to precise destinations within our bodies, and apply this knowledge to the design of "biologically-controlled" nanodevices for improved delivery of therapeutic agents to specific disease sites (Figure 1).

A plethora of promising tools are becoming available to tackle health problems, such as new drug carriers or delivery systems, macromolecular assemblies within the nanoscale-size range which can be loaded with diagnostic and therapeutic agents to improve their solubility, dosage, circulation, biodistribution and, hence, overall performance and safety. However, despite such a great advance and promise, our ability to treat diseases such as neurological maladies, genetic syndromes and cancer, remains a major challenge. One of the prime obstacles is



(Fig. 1) Targeted drug carriers for specific access within the body and its cells. Pictures are reproduced or adapted from the following sources (Copyrights reside on the respective publishers and associated professional societies): [1] Mane et al. (2012) Int J Nanomedicine, 7:4223-4237; [2] Garnacho et al. (2008) J Pharm Exp Ther, 325(2):400-408; [3] Finikova et al. (2008) Chem Phys Chem, 9(12):1673-1679; [4] Hsu et al. (2013) J Biomed Nanotech. 10(2):345-354; [5] Rosin et al. (2008) J Nucl Med, 49(1):103-111; [6] Ghaffarian et al. (2012) J Control Release, 163(1):25-33; [7] Serrano et al. (2012) Arterioscler Thromb Vasc Biol, 32(5):1178-1185; [8] Muro S. (2014) Adv Funct Mat, 24(19):2899-2906.

Postdocs
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Dencho Gututkov

PhD students
Maximilian Loeck

Masters student
Nuria Canal

Undergraduates
Milan Tump

our limited knowledge on the biological parameters that regulate the interaction of these systems with our tissues and, hence, our inability to gain non-invasive, efficient, and specific access within the body, its cells, and subcellular organelles. Our lab generates knowledge and tools aimed to improve our ability to deliver therapeutic agents to specific disease sites. Focusing on endothelial cell adhesion molecules as examples of accessible targets and on genetic conditions which serve as models for metabolic, neurodegenerative and cardiovascular syndromes, our ultimate goal is to enable effective treatment for these life-threatening disorders and other maladies characterized by similar pathological traits. Some of our main programmatic efforts are described below.

Biologically-Controlled Transport of Drug Carriers

How drug delivery systems are sensed, transported, and disposed of within the body, which is greatly dependent upon biological properties and processes, is far from being understood and much less controlled. Most targeted strategies are designed to achieve specific binding of drug delivery systems to cell-surface receptors, but then they simply depend on the signaling and transport processes the bound receptor regulates in nature. Instead, by deciphering the biological bases of these events, we impart the drug carrier control over biological signaling events independently from the receptor being bound, bypassing the mechanisms, kinetics, and destinations otherwise associated with these receptors. This provides a new and complementary avenue at the interface between the use of novel technological tools to decipher the biological mechanisms that regulate health and fail in disease, and the use of biological knowledge to optimize nanotechnology tools aimed to diagnose and treat human pathologies. For instance, we have shown how even using the same targeting or receptor, the kinetics, mechanism, and destination of a drug carrier can be modulated by: (a) varying its size, shape, and targeting valency; (b) varying the receptor epitope to which the carrier binds; (c) using auxiliary drugs to modulate the endocytic machinery; (d) coupling carriers to signaling molecules that can tune the uptake route independently from the receptor being used (Figure 2); (e) combining targeting to several receptors; or (f) coupling targeting moieties with anti-phagocytic moieties on the surface of drug carriers.

Transport of Drug Carriers Across Physiological Barriers

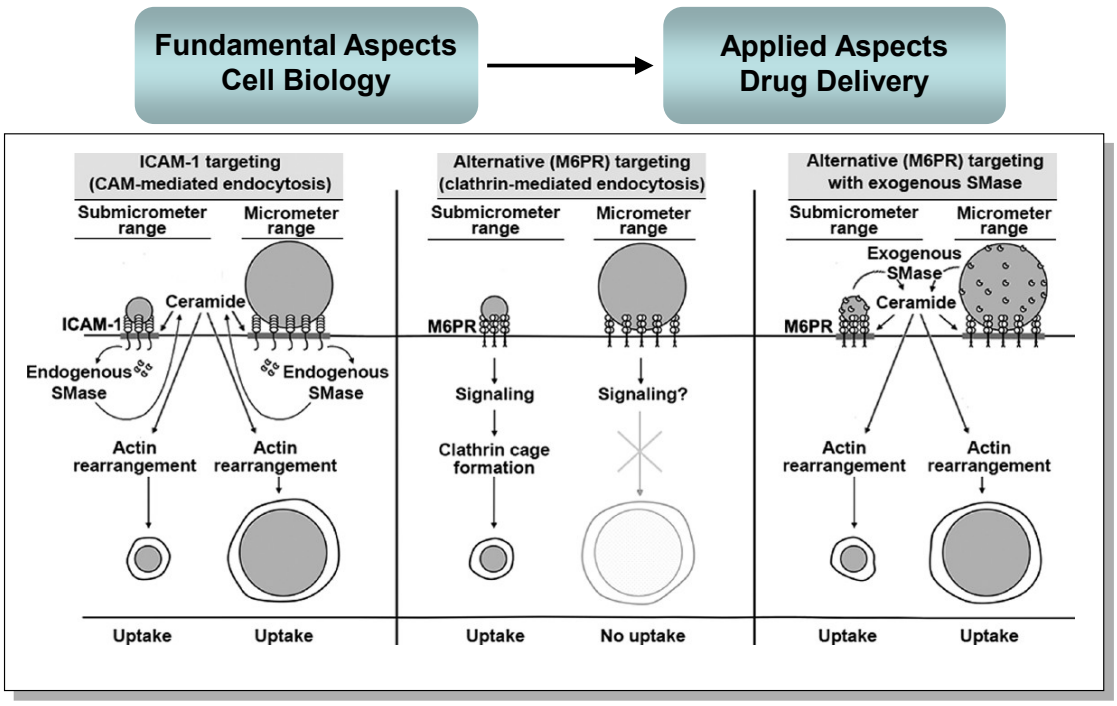
Crossing the linings that separate body and cellular compartments is paramount for efficient drug delivery. For instance, an epithelial barrier separates the gastrointestinal tract from the bloodstream, controlling uptake of orally ingested substances. While certain chemical entities are able to cross this barrier, many therapies do not and their successful utilization needs of means to bypass this obstacle. As for neurodegenerative conditions, they remain largely untreatable because

PUBLICATIONS

- Shuvaev V, Kiseleva R, Arguiri E, Villa C, Muro S, Christofidou-Solomidou M, Stan R, Muzykantov V. (2018) Targeting superoxide dismutase to endothelial caveolae profoundly alleviates inflammation caused by endotoxin. J Control Release. 272:1-8.
- Muro S. (2018) Alterations in cellular processes involving vesicular trafficking and implications in drug delivery. Biomimetics. 3(3), 19.

Targeted therapeutics and nanodevices

the vast majority of available pharmaceuticals and drug carriers under development both fail to traverse the endothelial barrier that separates the bloodstream from the brain tissue. Another example is that of novel biological therapeutics, which have demonstrated potential to manipulate disease targets far more precisely than their small chemical counterparts. However, these large and fragile therapeutics fail to traverse the membranes that separate the extracellular environment from the intracellular milieu and those of intracellular organelles. We demonstrated that the ICAM-1 pathway (described in the next section) enables transcytosis across epithelial and endothelial linings, which we explore for oral delivery and delivery across the blood-brain barrier. We were also able to target DNA-built dendrimers to cells specifically, whereby these DNA dendrimers enabled endosomal escape and cytosol delivery of a variety of cargoes, including small toxins, carbohydrates (Figure 3), proteins, and nucleic acids.



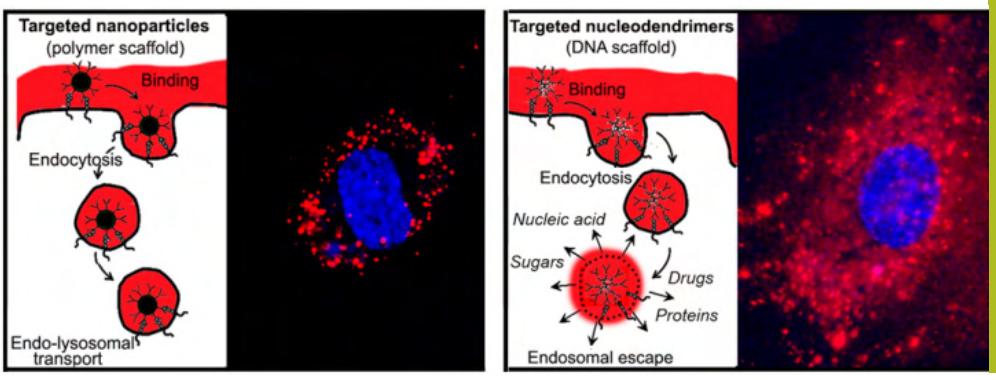
(Fig. 2) Enzyme-functionalization of drug carriers to improve their uptake by cells. ICAM-1-targeted nano- and micro-carriers are both internalized by cells due to natural sphingomyelinase (SMase)-dependent generation of ceramide at ICAM-1-binding sites. Ceramide improves carrier engulfment and membrane invagination, and acts as a second messenger toward actin re-organization, helping endocytic uptake (left panel). In contrast, targeting drug carriers to receptors associated with more size-restrictive pathways, e.g., clathrin-associated mannose-6-phosphate receptor (M6PR), often enables uptake of nano- but not micro-carriers (middle panel). Surface-functionalization of M6PR-targeted carriers with elements mimicking the ICAM-1 pathway, namely exogenous SMases (such as NSM), supplies the necessary ceramide and actin re-organization, improving endocytosis of nano- and micro-carriers even when targeted to receptors different from ICAM-1 (right panel). Reproduced from Ansar et al. (2013) ACS Nano, 7(12):10597-10611.

Vesicular Transport of Endothelial Cell Adhesion Molecules

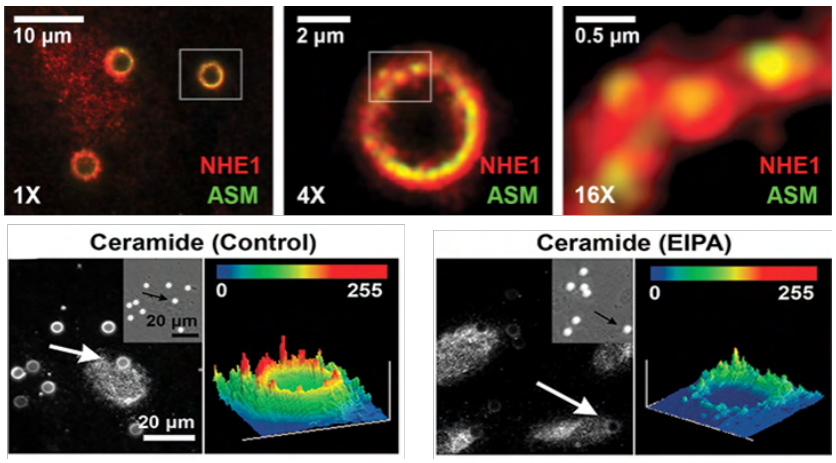
During my postdoctoral training, I helped to identify an endocytic pathway induced upon multivalent engagement of the endothelial cell-surface molecules ICAM-1 and PECAM-1. This new transport route is different from most others classically utilized for drug delivery, including clathrin-, caveolar-, macropinocytosis-, or phagocytosis-mediated pathways. My independent laboratory continues to unravel the regulation of this route, particularly focusing on ICAM-1 (Figure 4), and its implications in patho-physiology and drug delivery. The relevance of this new pathway is illustrated by the fact that ICAM-1 mediates extravasation of leukocytes during inflammation, signaling at the immune synapsis, and invasion by some pathogens (e.g., human rhinoviruses). The understanding of this fundamental route and its properties is also advancing diverse drug delivery applications by our group and many others.

Improving Treatment of Lysosomal Disorders

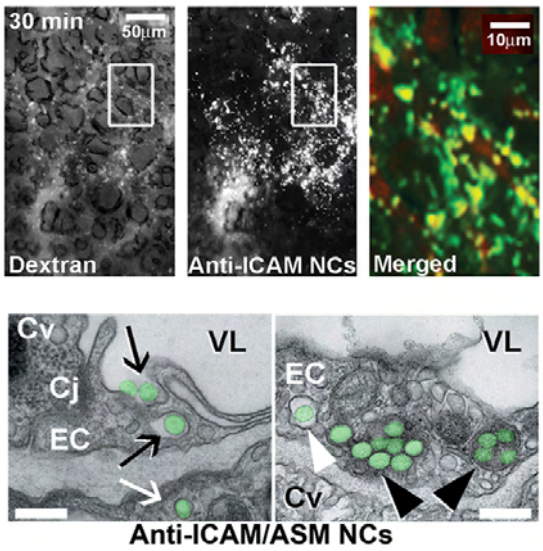
Monogenic pathologies due to genetic deficiency, such as the case of lysosomal disorders, are valuable models to study disease progression and therapeutic intervention because they have well-known etiology and defined molecular, biochemical and cellular effects, and because patient samples, diverse cell types, and small and large animal models are all readily available. Also, their unequivocal diagnosis enables the tracing of their progression from early to late stages. Since these diseases present with either acute or long-term effects depending on genetic severity, and associate with neurodegeneration, cardiovascular, metabolic, and cancer-like syndromes, they represent excellent disease models. The current lack of efficient therapies to treat these syndromes stems from problems similar to those described above, i.e. our inability to deliver therapeutics to disease sites in need. Consequently, we are applying targeted nanotechnology concepts to the treatment of genetic lysosomal disorders. Current therapies by i.v. enzyme infusion are only helpful for diseases where clearance cells and organs (liver, spleen, macrophages, etc.) are the main targets. Yet, delivery to other organs (brain, lungs, etc.) hinders translation for most diseases. Using types A and B Niemann-Pick (Figure 5), Fabry, and Gaucher diseases as examples, we have shown improved delivery of therapeutic enzymes to all affected organs in animal models, holding considerable translational potential.



(Fig. 3) Subcellular distribution of cargo delivered by targeted DNA-built dendrimers. (Left) Illustrative cartoon and corresponding microscopy showing that fluorescent dextran delivered to cells via targeted polymer nanoparticles resides in vesicular compartments (bright red spots) around the cell nucleus (blue). (Right) Instead, much dextran can escape vesicular compartments and reach the cytosol (more diffuse red color) when delivered using similarly targeted "nucleodendrimers" (DNA-built dendrimers). Adapted from Muro (2014) Adv Funct Mat, 24(19):2899-2906.



(Fig. 4) Cell adhesion molecule (CAM)-mediated endocytosis (Top) Different magnifications of microscopy images showing precise co-localization of sodium-proton exchanger 1 (NHE-1; red) and acid sphingomyelinase enzyme (ASM; green) at plasmalemma areas where ICAM-1-targeted carriers are being engulfed by cells. (Bottom) Relative enrichment of ceramide in regions of binding of ICAM-1-targeted carriers to control cell versus cell treated with EIPA (an NHE-1 inhibitor) shows that NHE-1 function is needed for membrane engulfment of said carriers. Adapted from Serrano et al. (2012) Arterioscler Thromb Vasc Biol, 32(5):1178-1185.



(Fig. 5) Endocytosis and lysosomal trafficking of anti-ICAM/ASM NCs in mouse lungs. (Top) Polymer nanocarriers (NCs) bearing therapeutic acid sphingomyelinase (ASM) and targeted to ICAM-1 were observed by fluorescent microscopy to abundantly reach the lungs, as observed 30 min after i.v. injection in mice (green spots). (Bottom) Transmission electron microscopy of lungs collected 3 h after i.v. administration confirmed the presence of NCs (green) interacting with endothelial cells (ECs). For instance, NCs can be seen being engulfed by cells (black arrows), within cell endosomes (white arrowheads) and lysosomes (black arrowheads), and transcytosed across the endothelium into subjacent epithelial cells (white arrow). VL = vessel lumen. Cv = caveolar vesicles. Cl = clathrin vesicles. Cj = cell junction. Scale bars = 300 nm. Reproduced from Garnacho et al. (2017) Mol. Ther. doi: 10.1016/j.ymthe.2017.05.014.

RESEARCH PROJECTS

- Controlling the differential transport of therapeutic cargoes into versus across the BBB (2018-2020)
  PI: **Silvia Muro** | *Ministerio de Ciencia, Innovación y Universidades*

- Targeted replacement of defective lysosomal enzymes in the lung and brain (2017-2021)
  PI: **Silvia Muro** | *NIH 2R01 HL098416*

- Characterization of cellular interactions and PK of targeted 3DNA carriers (2017-2020)
  PI: **Silvia Muro** | *Genisphere LLC*

- Synthetic nanobots to overcome physical barriers to enhance therapeutic efficacy (2017-2020)
  PI: **Brigitte Städler** | *Carlsberg CF16-0233*

- Development of nanoparticulate delivery system for anti-RAS protein therapeutics (2015-2019)
  PI: **Silvia Muro** and **Alexander Andrianov** | *MPower UMD*

- Peptides for transport of therapeutics and their carriers in mouse models and humans (2018-2019)
  PI: **Silvia Muro** | *UM Ventures*

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- **Dr. Robert Getts,** Genisphere LLC, Hatfield, PA, USA
- **Dr. Hamid Ghandehari,** University of Utah, UT, USA
- **Dr. Joe Kao,** University of Maryland Baltimore, MD, USA
- **Dr. Peter Kofinas,** University of Maryland College Park, MD, USA
- **Dr. Juan Marugan and Dr. Wei Zheng,** National Institutes of Health, Rockville, MD, USA
- **Dr. Vladimir Muzykantov,** University of Pennsylvania, Philadelphia, PA, USA
- **Dr. Gianfranco Pasut,** University of Padova, Padova, Italy
- **Dr. Josep Samitier,** Institute for Bioengineering of Catalonia, Barcelona, Spain (page 61)
- **Dr. Edward Schuchman,** Mount Sinai School of Medicine, New York, NY, USA
- **Dr. Brigitte Städler,** Aarhus University, Denmark

EQUIPMENT AND TECHNIQUES

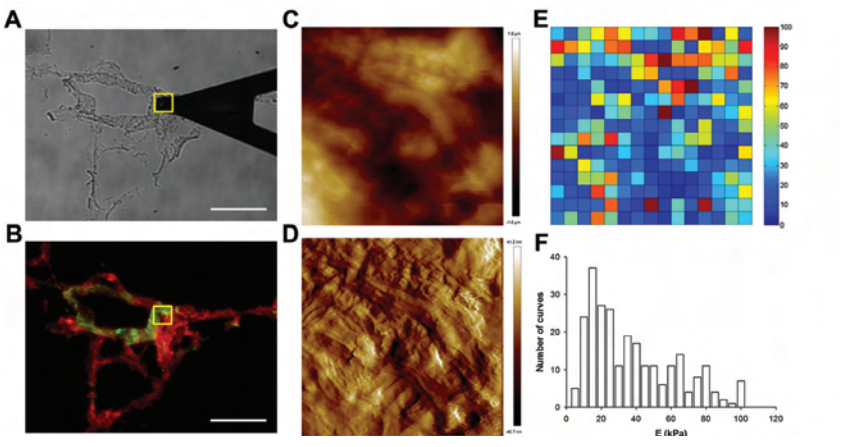
- Dynamic light scattering & ζ-potential
- Gel Permeation Chromatography
- Lyophilizer
- Rotovap
- Microsonicator
- Biosafety level 2 culture hoods
- CO2 incubators
- Liquid nitrogen storage tank
- Thermocycler
- Confocal-epifluorescence microscope
- Spectrofluorometer

Cellular and respiratory biomechanics
Daniel Navajas

The goal of our research is to gain a deeper understanding of cellular and respiratory biomechanics to improve the diagnosis and treatment of respiratory diseases.

The work is organized in two interrelated areas, focused on respiratory mechanics at both the systemic and the cellular level. We use basic and translational approaches in a multidisciplinary framework involving close cooperation with clinical groups.

Our current research interest is focused on the study of cell-matrix mechanical cross-talk for tissue engineering and regenerative medicine. Cells sense and actively respond to the biophysical features of their microenvironment. Mechanical properties of the extracellular matrix regulate critical cell processes such as contraction, migration, proliferation, gene expression and differentiation. We use atomic force microscopy and other cutting-edge biophysical techniques to study the mechanical properties of the extracellular matrix and their impact in cell behavior. We have implemented protocols to decellularize different soft tissues. This innovative approach allowed us to reveal the local mechanical properties of the lung and heart extracellular matrix. By seeding cells in these scaffolds we study the impact of the mechanical features of the microenvironment on stem cell engraftment and differentiation onto lung and heart phenotypes. We produce lab-on-chip devices mimicking the native cell microenvironment to investigate mechanical signaling driving stem cell differentiation under precisely controlled conditions. Using 3D bioprinters we integrate stem cells into synthetic and extracellular matrix hydrogels to fabricate tissue patches as an innovative approach to regenerate ventricular scars resulting from heart infarct. Organ biofabrication reengineered from decellularized tissue scaffolds offers a promising alternative for transplantation. We develop improved bioreactors mimicking breathing and blood perfusion to biofabricate lungs by seeding stem cells into acellular lung scaffolds.



Mechanical mapping and imaging of the extracellular matrix of a slice of decellularized mouse lung obtained by the combination of bright field (A), immunofluorescence microscopy (B), and atomic force microscopy (C – F).

Postdoc
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PhD students
Ignasi Jorba

Research assistant
Esther Marhuenda

Lab assistant
Elisabet Urrea

RESEARCH PROJECTS

MatriMec Estudio multiescala de la mecánica no lineal de la matriz extracelular de pulmón (2018-2019)
PI: **Daniel Navajas**
MINECO - Proyectos I+D Excelencia

Acció instrumental de programes de recerca orientats: Cardiopoesi amb biomatrius per regenerar la cicatriu post infart: From bench to bedside (first-in-man trial) (2017-2019)
PI: **Daniel Navajas**
Pla Estratègic de Recerca i Innovació en Salut (PERIS)

SGR Grups de recerca consolidats (2017-2020)
PI: **Daniel Navajas**
AGAUR - SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya

Precondicionamento biofísico de células madre mesenquimales para el tratamiento de la lesión pulmonar aguda provocada por sobreventilación en modelo animal (2015-2018)
PI: **Daniel Navajas**
MINECO - ISCIII - FIS-Proyectos de investigación en salud

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Prof. J. M. Montserrat, Service of Pneumology, Hospital Clinic/IDIBAPS, Barcelona, Spain

Prof. Antoni Bayés-Genis, Institut del Cor dels Germans Trias I Pujol, Badalona, Spain

Prof. Daniel Weiss, Department of Medicine, University of Vermont

Prof. A. Artigas, Intensive Care Service, Hospital Parc Taulí, Sabadell, Spain

Mauricio Rojas, Scientific Director of the Simmons Center for Interstitial Lung Diseases, University of Pittsburgh

David Gozal, Chair of the Department of Pediatrics, University of Chicago Medical Center, Chicago, USA

PUBLICATIONS

Villanueva, J. A., Isetta, V., Montserrat, J. M., Navajas, D. and Farré, R. A portable continuous positive airway pressure device that can perform optimally under strenuous conditions. American Journal of Respiratory and Critical Care Medicine, 198 (7): 956-958 (2018).

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Cellular and respiratory biomechanics

EQUIPMENT AND TECHNIQUES

- Fluorescence resonance energy transfer (FRET) microscopy
- Confocal Microcopy
- Traction Microscopy
- Live cell fluorescence microscopy
- Cell stretching
- Cell culture
- Magnetic Tweezers
- Atomic Force Microscopy
- Surface Micro/Nano-patterning

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Menal, M. J., Jorba, I., Torres, M., Montserrat, J. M., Gozal, D., Colell, A., Piñol-Ripoll, G., Navajas, D., Almendros, I. and Farré, R. Alzheimer's disease mutant mice exhibit reduced brain tissue stiffness compared to wild-type mice in both normoxia and following intermittent hypoxia mimicking sleep apnea. Frontiers in Neurology, 9: Article 1 (2018).

Farré, N., Otero, J., Falcones, B., Torres, M., Jorba, I., Gozal, D., Almendros, I., Farré, R. and Navajas, D. Intermittent hypoxia mimicking sleep apnea increases passive stiffness of myocardial extracellular matrix. A multiscale study. Frontiers in Physiology, 9: Article 1143 (2018).

Farré, N., Jorba, I., Torres, M., Falcones, B., Martí-Almor, J., Farré, R., Almendros, I. and Navajas, D. Passive stiffness of left ventricular myocardial tissue is reduced by ovariectomy in a post-menopause mouse model. Frontiers in Physiology, 9: Article 1545 (2018)

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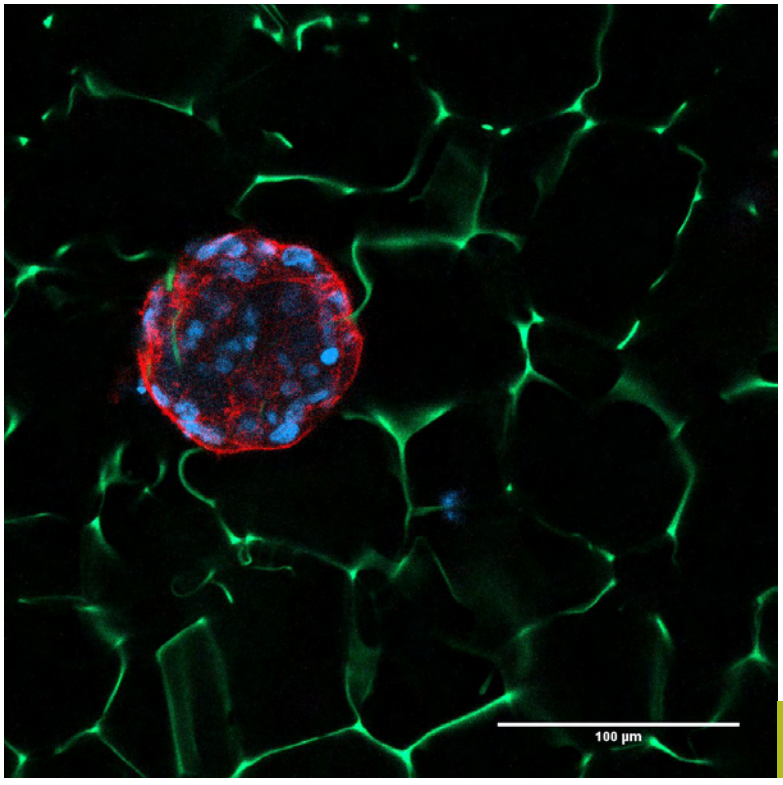
Biosensors for bioengineering
Javier Ramón

Drug discovery pathway relies heavily on in vivo animal models and in vitro cell mediums. In the case of animal models we have not only some ethical problems but also the ability to extrapolate data to human conditions is limited and in vitro platforms often do not simulate the complex cell–cell and cell–matrix interactions crucial for regulating cell behaviour.

Biosensors for bioengineering group is focused in a new line of research that has become of extreme importance in the last years. The idea is to integrate biosensor technology and nanotechnology with stem cell research and with tissue engineering. Engineered tissues are integrated with biosensing technology to obtain microdevices for detecting cellular responses to external stimuli, monitoring the quality of the microenvironment (e.g., metabolites, nutrients), and supporting diverse cellular requirements. This research on 3D-functional engineered tissues is expected to develop knowledge of tissue construction and their functions and relation with some human diseases. Integration of fully functional tissues with microscale biosensor technology allowed us to obtain "organs-on-a-chip". These chips could be used in pharmaceutical assays and could be a step toward the ultimate goal of producing in vitro drug testing systems crucial to the medicine and pharmaceutical industry.



Pancreas islet stained in blue for nuclei and red for actin inside a microporous microfibrillated cellulose-gelatin scaffold stained with green.

Biosensors for bioengineering

Postdocs
Irene Marco
Maria Alejandra Ortega

PhD students
Laura Clua
Xiomara Gislen Fernández
Ferran Velasco

Masters students
Wael Jamous

Undergraduates
Natalia Kovaleva
Elodie Medina

Lab technician
Francesco De Chiara
Albert Garcia

Lab assistants
Jordina Balaguer
Nerea Murillo

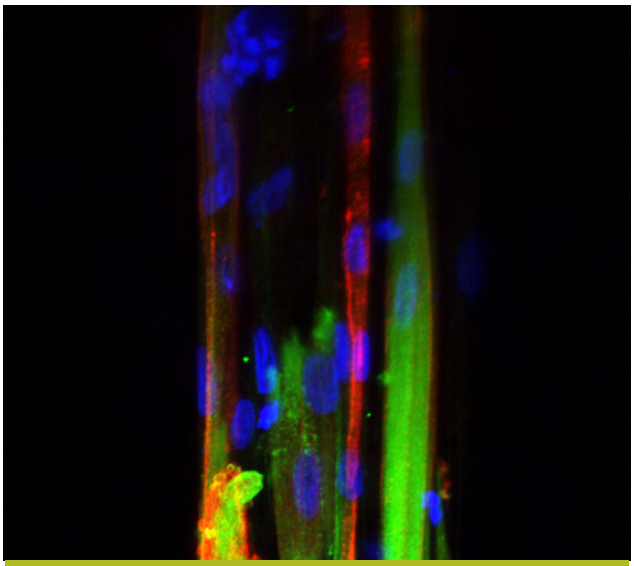
Visiting researchers
Seongsu Eom
Juanma Fernandez
Minseong Kim

RESEARCH PROJECTS

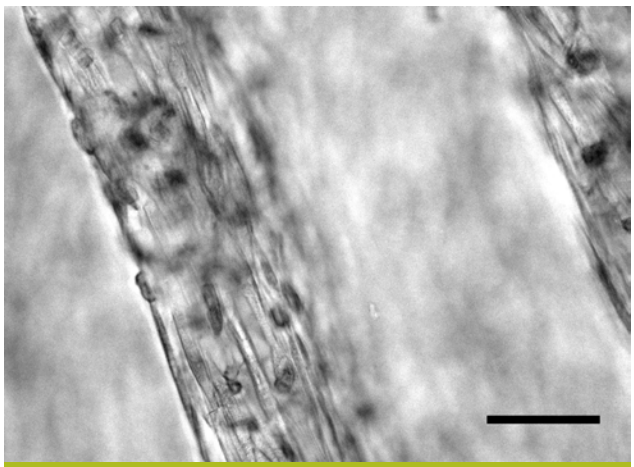
TATAMI Therapeutic targeting of MBNL microRNAs as innovative treatments for myotonic dystrophy
PI: **Javier Ramón**
Fundación Bancaria "La Caixa" – CaixaHealth programme

DAMOC Diabetes Approach by Multi-Organ-on-a-Chip
PI: **Javier Ramón**
European Commission (H2020) – ERC Starting Grant

INDUCT Fabrication of a biomimetic in vitro model of the intestinal tube muscle wall: smooth muscle-on-a-chip
PI: **Javier Ramón**
MINECO Retos investigación: Proyectos I+D/TEC2017-83716-C2-2-R



Engineered skeletal muscle from patients' cells with myotonic dystrophy disease.



Human myotubes encapsulated in micropatterned hydrogel scaffold. Scale is 100 µm.

PUBLICATIONS

García-Lizarribar, A., Fernández-Garibay, X., Velasco-Mallorquí, F., Castaño, A. G., Samitier, J. and Ramon-Azcon, J. Composite biomaterials as long-lasting scaffolds for 3D bioprinting of highly aligned muscle tissue. Macromolecular Bioscience, 18 (10): 1800167 (2018).

Conference Paper

de Goede, M., Chang, L., Dijkstra, M., Obregón, R., Ramón-Azcon, J., Martínez, E., Padilla, L., Adan, J., Mitjans, F. and García-Blanco, S. M. Al2O3 Microresonator based passive and active biosensors. 20th International Conference on Transparent Optical Networks. Bucharest, Romania (2018). Published by IEEE Computer Society (2018/07/01).

de Goede, M., Chang, L., Dijkstra, M., Obregón, R., Ramón-Azcon, J., Martínez, E., Padilla, L., Adan, J., Mitjans, F. and García-Blanco, S. M. Al2O3 Microresonator based passive and active biosensors. 20th International Conference on Transparent Optical Networks. Bucharest, Romania (2018). Published by IEEE Computer Society (2018/07/01).

COLLABORATIONS

Academy:

Prof. Josep Samitier, Institute for Bioengineering of Catalonia (IBEC) (page 61)

Dr. Elena Martínez, Institute for Bioengineering of Catalonia (IBEC) (page 36)

Dr. Eduard Montanya, Head Diabetes Section, Bellvitge, Senior Professor, University of Barcelona | UB · Department of Clinical Sciences

Dr. Rosa Gasa, Translational research in Diabetes, Lipids and Obesity Institut D´Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Spain

Dr. Anna Novials, Pathogenesis and prevention of diabetes Institut D´Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Spain

Dr. Isabel Illa Sendra, Neuromuscular Barcelona group Directora de la Unidad de Enfermedades Neuromusculares (ENM) del Servicio Neurología del Hospital Santa Creu i Sant Pau (HSCSP) de Barcelona, Spain

Dr. Ruben Artero, Translational Genomic Group Instituto de Investigación Sanitaria de Valencia (INCLIVA), Spain

D**r. Ignacio Perez de Castro**, Instituto de Salud Carlos III | ISCIII · Human Genetics, Spain

Industry:

Novo Nordisk

Multiwave

Oxford Instrument

Patients associations:

Spanish Federation of Neuromuscular diseases (ASEM)

Fundación Andrés Marcio

EQUIPMENT AND TECHNIQUES

Micro and nanofabrication techniques:
- 3D microstructures on hydrogel materials
- Mini-bioreactor for 3D cell culture
- Microelectrodes fabrication
- Synthesis and chemical modification of polymers and surfaces
- Dielectrophoretic cells and micro particles manipulation

Characterization techniques:
- Optical Microscopes (white light/epifluorescence)
- Electrochemical techniques (Potentiometric/ Amperometric/Impedance spectroscopy)
- Immunosensing techniques (Fluorescence ELISA/ Colorimetric ELISA/magneto ELISA)

Equipment:
- Microfluidic systems (High precision syringe pumps/ Peristaltic pumps/Micro valves)
- Biological safety cabinet (class II)
- Epifluorescence microscope for live-cell imaging

Access to the Nanotechnology Platform (IBEC Core Facilities): equipment for hot embossing lithography, polymer processing and photolithography, chemical wet etching, e-beam evaporation and surface characterization (TOF-SIMS)

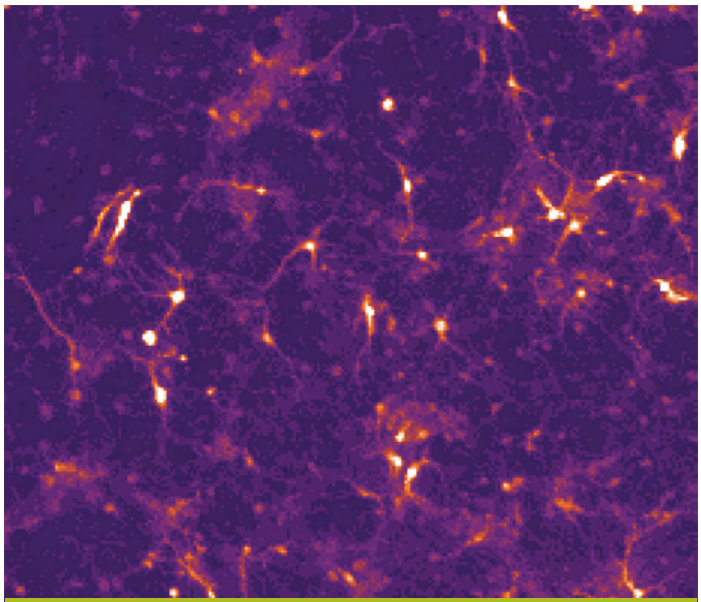
Access to the Scientific and Technological Centers (University of Barcelona): equipment for surface analysis (XPS, AFM, XRD), organic structures characterization (NMR) and microscopy techniques (SEM, TEM, confocal)

Molecular and Cellular Neurobiotechnology
José Antonio del Río

Our research interests are focused on three main aspects of developmental neurobiology and neurodegeneration

1) Development of new lab on chip devices for neurobiological research

One of our focus is to mimic the developing and neurodegenerating nervous system in lab on chip devices. We believe that combining several different stimuli in the chip resembles a more realistic environment that nerve cells will encounter in the living animal in normal and disease conditions. These experiments using Lab-on-a-Chip models in turn will make future studies on the role of neuronal cells in development and regeneration more accurate and complete. Thus, we developed a new device able to reproduce the formation of the neuromuscular junction (NMJ) in lab on chip devices. In addition, a device designed to analyse axon lesions of cortical neurons was also developed. Current experiments of our group in collaboration with groups of IBEC, CIBER-BBN, and other labs aimed at developing new lab on chip devices to mimics and modulate particular neurobiological processes. For example: i) on chip lab platform to monitor drug delivery modulating neuronal activity (see figure); ii) cortico-spinal chips to develop axon regenerative studies of new drug formulation (in collaboration with Imperial College; London); iii) devices to molecular gradient generation for migrating neurons (in collaboration with i3A, Zaragoza) and, iv) in silico 3D modeling for neurodegenerative diseases (Alzheimer and Parkinson chip). Last experiments are focused to reproduce a lab on chip devices to analyse and to reproduce ALS models (in collaboration with Biodonostia Hospital) (Figure 2)



(Fig. 1) Calcium waves in cultured cortical neurons growing on compartimentalized lab on chip devices.

Senior researcher
Rosalina Gavín

Postdocs researcher
Vanessa Gil
Arnau Hervera

PhD students
Laia Lidón
Ana López
Andreu Matamoros
Francina Mesquida
Júlia Sala

Lab technician
Miriam Segura

Masters student
Nuria Planas

Visiting researcher
Daniela Del Valle Díaz

2) New strategies to avoid a-synuclein and tau transport in neurons

α-Synuclein is a key player in the pathogenesis of synucleinopathies, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Transmission of synthetic α-synuclein aggregates has been demonstrated in several cellular and animal models. Several groups have reported that insoluble α-synuclein shows "prion-like" propagation in wild-type mice. However, the basis of the spreading process remains poorly understood although cell to cell transport via exocytosis has been proposed. We described in 2018 that PrPC is a new receptor for α-synuclein involved in their spreading and propagation. Our new objectives aimed to block this interaction to reduce the neuropathological transport of α-synuclein. Similar experiments are also developed in the case of tau, one of the hallmarks of Alzheimer´s disease, since tau also binds to PrPC during its inter-neuronal propagation.

(Fig. 2) Example of a monolayer of ChR2-expressing C2C12 myotubes on compartmentalized lab on chip devices showing the traction vector forces during cell contraction after 470 nm light stimulation.

3) New approaches to enhance axon regeneration after lesion

Following axonal lesions in the adult CNS, damaged axons degenerate, while surviving fibres are unable to regenerate, and have a limited capacity to sprout and to re-establish lost connections. Experimental evidence suggests that providing a permissive extracellular environment containing cellular or biomaterial bridges is not enough to increase axon regrow to obtain functional regeneration, supporting the importance of clarifying the complex transcriptional response below these signalling pathways. As an alternative, activating or recapitulating the developmental program of the lesioned neuron to

PUBLICATIONS

■ Hervera, A., De Virgiliis, F., Palmisano, I., Zhou, L., Tantardini, E., Kong, G., Hutson, T., Danzi, M. C., Perry, R. B. T., Santos, C. X. C., Kapustin, A. N., Fleck, R. A., Del Río, J. A., Carroll, T., Lemmon, V., Bixby, J. L., Shah, A. M., Fainzilber, M. and Di Giovanni, S. Reactive oxygen species regulate axonal regeneration through the release of exosomal NADPH oxidase 2 complexes into injured axons. Nature Cell Biology, 20 (3): 307-319 (2018).

■ Del Río, J. A., Ferrer, I. and Gavín, R. Role of cellular prion protein in interneuronal amyloid transmission. Progress in Neurobiology, 165-167 87-102 (2018).

■ Urrea, L., Segura, M., Masuda-Suzukake, M., Hervera, A., Pedraz, L., Aznar, J. M. G., Vila, M., Samitier, J., Torrents, E., Ferrer, I., Gavín, R., Hagesawa, M. and Del Río, J. A. Involvement of cellular prion protein in α-synuclein transport in neurons. Molecular Neurobiology, 55 (3): 1847-1860 (2018).

sprout and regenerate may represent a complementary therapeutic approach and may sometimes directly counteract the inhibitory signalling. Optogenetics is currently the state-of-the-art method for activity-based nervous system research, allowing more specific cellular stimulations by light in a less invasive techniques compared to classical electrical stimulation, but leading to a more tailored physiological responses. In our laboratory, we started to analyse whether optical stimulation of lesioned neurons is able to enhance axonal growth or sprouting. These experiments were performed on lesioned cortical neurons and *in vivo*.

RESEARCH PROJECTS

ANGIODEVSNC Funciones de genes implicados en angiogénesis y remodelación vascular durante el desarrollo cortical y en neurodegeneración
PI: **José Antonio Del Río** | *MINECO Retos investigación: Proyectos I+D/BFU2015-67777-R*

Role of the cellular prion protein as "cross-talk" protein between a-syn/ LRRK2 and p-Tau in sporadic and familiar Parkinson´s disease
PI: **José Antonio Del Río** | *Fundació La Marató de TV3 TV3-Projectes de recerca La Marató TV3/20143410*

ANGIODEVSNC SGR Grups de recerca consolidats 2017-2019
PI: **José Antonio Del Río** | AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 648

COLLABORATIONS

Dr. Adolfo Lopéz de Munain, Hospital de Donostia, San Sebastian, Spain

Dr. Joaquin Castilla, CiC Biogune, Bilbao, Spain

Prof. Juan María Torres, INIA-CISA CSIC, Valdeolmos, Madrid, Spain

Prof. José María Delgado and **Prof. Agnest Gruart**, UPO, Sevilla, Spain

Prof. Jose Manuel García Verdugo, Facultad de Ciencias, Universidad de Valencia, Spain

Prof. Jose Manuel García Aznar, Nanotechnology Institute i3A, Zaragoza, Spain

Prof. Fernando Albericio and **Ernest Giralt**, Institute for Research in Biomedicine (IRB), Barcelona

Matamoros-Angles, A., Gayosso, L. M., Richaud-Patin, Y., Di Domenico, A., Vergara, C., Hervera, A., Sousa, A., Fernández-Borges, N., Consiglio, A., Gavín, R., López de Maturana, R., Ferrer, I., López de Munain, A., Raya, A., Castilla, J., Sánchez-Pernaute, R. and Del Río, J. A. iPS cell cultures from a Gerstmann-Sträussler-Scheinker patient with the Y218N PRNP mutation recapitulate tau pathology. Molecular Neurobiology, 55 (4): 3033-3048 (2018).

Llorens, F., Thüne, K., Martí, E., Kanata, E., Dafou, D., Díaz-Lucena, D., Vivancos, A., Shomroni, O., Zafar, S., Schmitz, M., Michel, U., Fernández-Borges, N., Andréoletti, O., del Río, J. A., Díez, J., Fischer, A., Bonn, S., Sklaviadis, T., Torres, J. M., Ferrer, I. and Zerr, I. Regional and subtype-dependent miRNA signatures in sporadic Creutzfeldt-Jakob disease are accompanied by alterations in miRNA silencing machinery and biogenesis. PLoS Pathogens, 14 (1): e1006802 (2018).

Garcia-Esparcia, P., Koneti, A., Rodríguez-Oroz, M. C., Gago, B., del Rio, J. A. and Ferrer, I. Mitochondrial activity in the frontal cortex area 8 and angular gyrus in Parkinson's disease and Parkinson's disease with dementia. Brain Pathology, 28 (1): 43-57 (2018).

Ferrer, I., García, M. A., González, I. L., Lucena, D. D., Villalonga, A. R., Tech, M. C., Llorens, F., Garcia-Esparcia, P., Martinez-Maldonado, A., Mendez, M. F., Escribano, B. T., Serra, J. J. B., Sabido, E., de la Torre Gómez, C. and del Rio, J. A. Aging-related tau astrogliopathy (ARTAG): Not only tau phosphorylation in astrocytes. Brain Pathology, 28 (6): 965–985 (2018).

Dr. Miriam Royo, Consejo Superior de Investigaciones Científicas (CSIC), Barcelona, Spain

Dr. Elisabeth Engel (page 13), **Prof. Josep Samitier,** (page 61), **Prof. Xavier Trepat,** (page 75) and **Prof. Daniel Navajas,** (page 48) Institute for Bioengineering of Catalonia (IBEC), Spain

Prof. Ángel Raya, Center of Regenerative Medicine in Barcelona (CMRB), Spain

Dr. Antonella Consiglio and **Dr. Franc Llorens**, Institut d'Investigació Biomèdica de Bellvitge, University of Barcelona, Spain

Prof. Jesús Ávila and **Prof. Francisco Wandosell**, Consejo Superior de Investigaciones Científicas (CSIC), Universidad Autónoma de Madrid, Spain

Prof. Isidro Ferrer, Institut d'Investigació Biomèdica de Bellvitge, University of Barcelona, Spain

Dr. Alberto Lleó, Hospital Sant Pau, Barcelona, Spain

Prof. Miquel Vila, VHIR, Barcelona, Spain

Prof. Fanny Mann, Developmental Institute of Marseille Luminy, Université de la Méditerranée, Marseille, France
Prof. Beth L. Pruitt, Mechanical engineering, Stanford University, USA

Prof. Masato Hagesawa, Faculty of Medicine, Tokyo

Prof. José Luis Lanciego, CIMA, Navarra, Spain

EQUIPMENT

- Neural stem cell culture
- Microscopy facility (Olympus BX61 and Olympus IX71 with LCi culture and OKOlab systems incubator)
- Optogenetic Pulser and Prizmatix LED source (in vitro)
- Electroporation system (BTX 600)
- Pressure microinjection system (Eppendorf)
- Protein expression and purification systems
- Technology of neuronal culture facilities (2D and 3D)
- Lentiviral/retroviral production and characterization
- Protein and DNA electrophoresis
- *In situ* hybridization oven
- Optogenetic *in vivo* stimulation system

Mata, A., Gil, V., Pérez-Clausell, J., Dasilva, M., González-Calixto, M. C., Soriano, E., García-Verdugo, J. M., Sanchez-Vives, M. V. and Del Río, J. A. New functions of Semaphorin 3E and its receptor PlexinD1 during developing and adult hippocampal formation. Scientific Reports, 8 (1): 1381 (2018).

Franco, R., Aguinaga, D., Reyes, I., Canela, E. I., Lillo, J., Tarutani, A., Hasegawa, M., del Ser-Badia, A., del Rio, J. A., Kreutz, M. R., Saura, C. A. and Navarro, G. N-methyl-D-aspartate receptor link to the MAP kinase pathway in cortical and hippocampal neurons and microglia Is dependent on calcium sensors and Is blocked by α-Synuclein, Tau, and phospho-Tau in non-transgenic and transgenic APPSw,Ind Mice. Frontiers in Molecular Neuroscience, 11 (273): Article 273 (2018).

Tomas-Roig, J., Piscitelli, F., Gil, V., Quintana, E., Ramió-Torrentà , L. I., del Río, J. A., Moore, T. P., Agbemenyah, H., Salinas, G., Pommerenke, C., Lorenzen, S., Beißbarth, T., Hoyer-Fender, S., Di Marzo, V. and Havemann-Reinecke, U. Effects of repeated long-term psychosocial stress and acute cannabinoid exposure on mouse corticostriatal circuitries: Implications for neuropsychiatric disorders. CNS Neuroscience & Therapeutics, 24 (6): 528-538 (2018).

Badiola-Mateos, M., Hervera, A., del Río, J. A. and Samitier, J. Challenges and future prospects on 3D in-vitro modeling of the neuromuscular circuit. Frontiers in Bioengineering and Biotechnology, 6 Article 194 (2018).

Cellular and molecular mechanobiology
Pere Roca-Cusachs

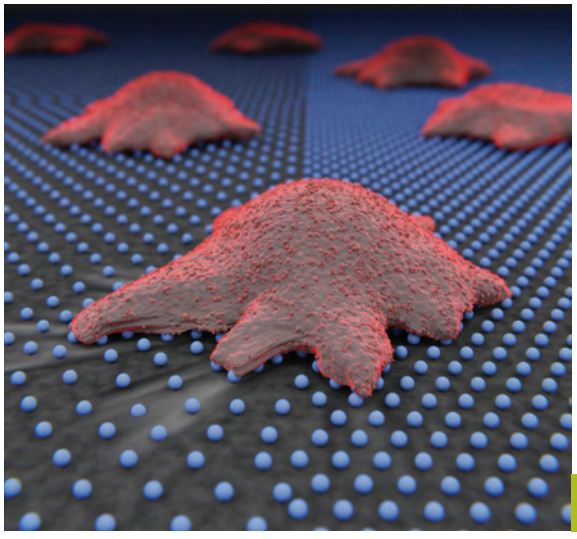
Every time we blink, move a hand, draw a breath, or walk, cells in our body exert, transmit, withstand, and detect forces. This mechanical interaction with the environment determines how cells proliferate, differentiate, and move, and regulates development, tumorigenesis or wound healing.

Just like biochemical stimuli initiate signaling cascades, mechanical forces affect the links and conformation of a network of molecules connecting cells to the extracellular matrix. Our research aims precisely at unraveling the mechanisms that these molecules use to detect and respond to mechanical stimuli like forces or tissue rigidity, triggering downstream cell responses.

To this end, we combine biophysical techniques like magnetic tweezers, Atomic Force Microscopy, traction microscopy, and microfabricated force sensors with molecular biology, advanced optical microscopy, and theoretical modelling.

Sensing rigidity: Using this multi-disciplinary approach, we have recently unveiled a molecular mechanism that cells employ to detect and respond to the rigidity of their environment, which could be crucial in breast tissue and breast cancer (Elosegui-Artola et al., 2016 Nat. Cell Biol., and Elosegui-Artola et al. 2014, Nature Mater.). This mechanism is mediated by what is known as a "molecular clutch": in a surprising analogy with a car engine, cells can be understood as a molecular network that can engage and disengage from its environment, just as the clutch of a car. This affects force transmission from the environment to cells, and also within different cell components. Recently, we have begun to explore how force transmission to the nucleus affects the dynamics of transcriptional regulators, such as YAP (Elosegui-Artola et al., 2017, Cell).

Sensing the environment: We are currently expanding on the idea of the molecular clutch, to explore how cell molecular engines sense not only mechanical rigidity, but other important parameters from their environment: for instance, the composition and distribution of ligands



Artistic rendering of a cell attaching to a substrate coated with a gold nano-pattern array, used to study how cells detect spatial cues (From Oria et al. 2017, Nature).

Postdocs
Ion Andreu
Laura Faure
Zanetta Zoi (Jenny) Kechagia
Anabel-Lise Le Roux

PhD students
Víctor González
Ignasi Granero
Xarxa Quiroga
Srivatsava Viswanadha Venkata Naga Sai

Lab assistant
Oriol Mañé

Research assistant
Marc Molina
Marina Pavlova

Visiting researchers
Dimitri Kaurin

in the extracellular matrix, or other cells. In this regard, we recently uncovered that this concept can explain how cells sense the spatial distribution of ligands in the extracellular matrix (Oria et al., Nature 2017). We have also demonstrated that cell-cell force transmission, mediated by a molecular clutch, is essential for cells to sense gradients in stiffness (Sunyer et al., Science 2016, in collaboration with the group of Xavier Trepat).

The membrane as a mechanosensor: Due to its mechanical properties, the plasma membrane itself can respond to forces and act as a mechanosensor. Recently, we have shown that cell membranes can use purely physical principles to adapt their shape in response to mechanical forces (Kosmalska et al., 2015, Nat. Commun.). We are currently studying how cells harness this physical membrane behavior to respond to signals from their environment.

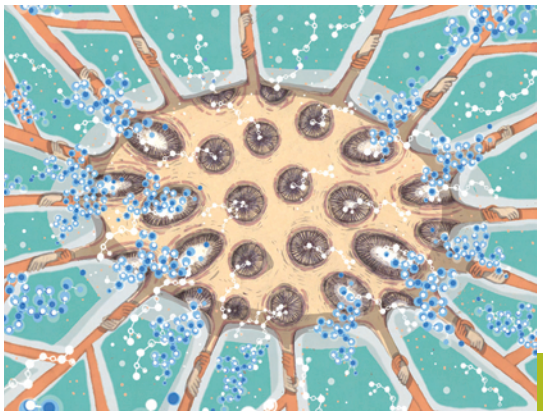
Ultimately, when we determine the molecular mechanisms that communicate cells with their environment, we will understand how forces determine development when things go right, and tumor formation when they go wrong.

RESEARCH PROJECTS

MECHANOMEMBRANE Redes mecanoquímicas en la membrana plasmática (2017-2018)
PI: **Pere Roca-Cusachs** | *MINECO - Subprograma Estatal de Generación de Conocimiento "EUROPA EXCELENCIA"*

IMREG El sistema acoplado entre integrinas y proteínas adaptadoras como regulador mecánico del comportamiento celular (2016-2019)
PI: **Pere Roca-Cusachs** | *MINECO - Proyectos I+D Excelencia*

Desarrollo de una terapia innovadora para el tratamiento de los tumores sólidos mediante la inhibición de la mecanotransducción (2018-2020)
PI: **Pere Roca-Cusachs** | *MINECO - Retos-Colaboración*



Cartoon depicting how force transmission to the nucleus affects nuclear pores, leading to nuclear protein import (from Elosegui-Artola et al. 2017, Cell).

PUBLICATIONS

Uroz, M., Wistorf, S., Serra-Picamal, X., Conte, V., Sales-Pardo, M., Roca-Cusachs, P., Guimerà, R. and Trepat, X. Regulation of cell cycle progression by cell–cell and cell–matrix forces. Nature Cell Biology, 20 (6): 646-654 (2018).

Elosegui-Artola, A., Trepat, X. and Roca-Cusachs, P. Control of mechanotransduction by molecular clutch dynamics. Trends in Cell Biology, 28 (5): 356-367 (2018)

Thottacherry, J. J., Kosmalska, A. J., Elosegui-Artola, A., Pradhan, S., Sharma, S., Singh, P. P., Guadamillas, M. C., Chaudhary, N., Vishwakarma, R., Trepat, X., del Pozo, M. A., Parton, R. G., Pullarkat, P., Roca-Cusachs, P. and Mayor, S. Mechanochemical feedback and control of endocytosis and membrane tension. Nature Communications, 9 4217 (2018).

Gauthier, N. C. and Roca-Cusachs, P. Mechanosensing at integrin-mediated cell–matrix adhesions: from molecular to

Cellular and molecular mechanobiology

Inhibiting mechanostransduction as a novel therapy in the treatment of solid tumors (2017-2018)
PI: **Pere Roca-Cusachs** | *Obra Social La Caixa - Caixaimpluse*

Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
PI: **Pere Roca-Cusachs** | *Obra Social La Caixa*

MECHANO-CONTROL Mechanical control of biological function (2017-2021)
PI: **Pere Roca-Cusachs** | *European Commission - FET Proactive*

TALVIN Inhibiting mechanotransduction for the treatment of pancreatic cancer (2018-2019)
PI: **Pere Roca-Cusachs** | *European Commission - FET Innovation Launchpad*

SGR Grups de recerca consolidats (2017-2020)
PI: **Pere Roca-Cusachs** | *AGAUR - SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya*

COLLABORATIONS

Dr. Nils Gauthier, Mechanobiology Institute, Singapore

Prof. Miguel Ángel del Pozo, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid

Prof. Marino Arroyo, UPC, Barcelona, Spain

Prof. Ada Cavalcanti, University of Heidelberg, Germany

Dr. Satyajit Mayor, National Centre for Biological Sciences, Bangalore, India

Dr. Sergi Garcia-manyes, King's College, London, UK

Dr. Cheng Zhu, Georgia Tech, Atlanta, USA

Dr. Louise Jones, Barts Cancer Institute, London, UK

EQUIPMENT AND TECHNIQUES

- Confocal Microcopy
- Traction Microscopy
- Live cell fluorescence microscopy
- Cell stretching
- Cell culture
- Magnetic Tweezers
- Atomic Force Microscopy
- Surface Micro/Nano-patterning
- Optical tweezers

integrated mechanisms. Current Opinion in Cell Biology, 50 20-26 (2018).

Bennett, M., Cantini, M., Reboud, J., Cooper, J. M., Roca-Cusachs, P. and Salmeron-Sanchez, M. Molecular clutch drives cell response to surface viscosity. Proceedings of the National Academy of Sciences of the United States of America, 115 (6): 1192-1197 (2018).

Roca-Cusachs, P. Cell scientist to watch - Pere Roca-Cusachs. Journal of Cell Science, 131 (16): jcs222596 (2018).

Escribano, J., Sunyer, R., Sánchez, M. T., Trepat, X., Roca-Cusachs, P. and García-Aznar, J. M. A hybrid computational model for collective cell durotaxis. Biomechanics and Modeling in Mechanobiology, 17 (4): 1037-1052 (2018).

Nanobioengineering
Josep Samitier

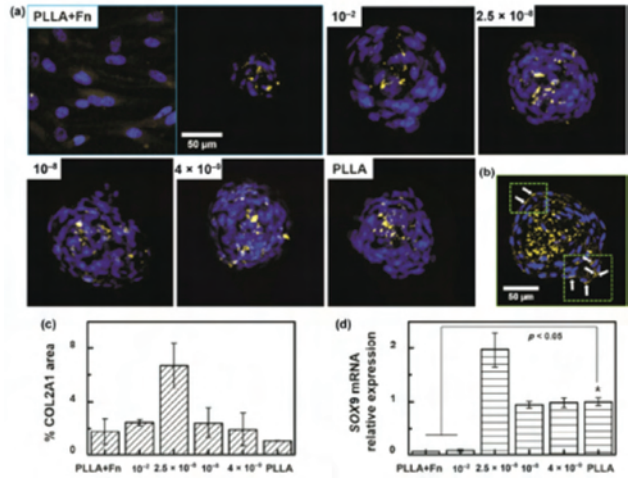
The Nanobioengineering group is a truly multidisciplinary team composed by researchers coming from very diverse backgrounds working together in applying nanotechnology for the development of new biomedical systems and devices, mainly for diagnostic purposes, and integrated microfluidic Organ-on-a-Chip devices for the study of organ physiology, disease etiology, or drug screening.

The main research activities of the group include the engineering and biochemical functionalization of biomaterials integrated with microfluidics systems. The bioengineered microdevices are used to study cell responses to biomolecular compounds applied to Organ-on-Chip devices, or for the development of new Lab-on-a-Chip based biosensors.

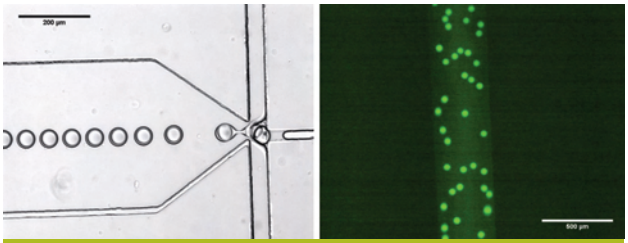
The goal is to fabricate microsystems containing living cells that recapitulate tissue and organ level functions in vitro and new portable diagnosis devices that can be used as Point-of-Care systems. The projects carried out by the group are focused on clinical and industrial problems and are related to three convergent research lines:

1) Biosensors and Lab-on-a-Chip devices for clinical diagnosis and monitoring

- DNA sensors-arrays integrated in lab-on-a-chip for portable point of care diagnosis
- Vascular implantable sensors for circular cancer biomarker detection
- Antibody-based sensors for pathogenic microorganisms' detection and neurodegenerative early detection
- Implantable physiological sensors-array for tissue in vivo hypoxia and ischemia monitoring



Chondrogenesis improvement by using nanoparticles to control cell adhesion and migration.



Microfluid chip for droplet generation and encapsulation.

Nanobioengineering

Senior researchers
Anna Lagunas
Mònica Mir
Joan Montero
Aranzazu Villasante

Postdocs
Romén Rodríguez
Maria José López
Lourdes Josefina Rivas
Loris Rizzello

PhD students
Enrico Almici
Maider Badiola
Ignasi Casanellas
Andrea García
Albert Manzano
Roberto Paoli
Jessica Sierra

Masters student
Noelia Hernández
Marc Tarin
Genis Rebost

Undergraduate
Sergi Casanova

Senior technician
Clara Alcon
Sam Dulay
Sandrine Miserere

- 3D printing microfluidic technology

- Microfluidic chip using hydrodynamic forces for cell counting and sorting. Application for detection of circulating tumours cells (CTCs)

2) Nanotechnology applied to biomolecule interaction studies and micro/nano-environments for regenerative medicine applications

- Development of bioengineered 2D and 3D micro/nanoenvironments with a topography and chemical composition controlled at the nanoscale for cell behavior studies (adhesion, proliferation, differentiation). Application to musculoskeletal system regeneration

- Biophysical description of cellular phenomena (adhesion, cell migration, differentiation) using micro/nanotechnologies, cell biology tools and soft matter physics

- Study of biological mechanisms at single molecule level

- Study of magnetite nanoparticles - Amyloid-Beta interaction in Alzheimer disease

3) Microfluidic systems for biological studies and Organ-on-Chip devices

- Microfluidic chip for blood/plasma filtering and anemia diseases characterization

- Spleen-on-a-chip development

- Nanoporous-based systems for Kidney-on–a-chip developments

- Engineering microfluidic platforms for neurobiological studies

- Development of 3D neuromuscular tissue models for soft robotics and clinical applications

- Microfluidic system to monitor cancer therapy response. Tumor Cancer on a chip in vitro development

- Microfluidic Vessel on-a-chip for screening drug delivery systems

PUBLICATIONS

- Katuri, J., Caballero, D., Voituriez, R., Samitier, J. and Sanchez, S. Directed flow of micromotors through alignment interactions with micropatterned ratchets. ACS Nano, 12 (7): 7282-7291 (2018).

- Hortigüela, V., Larrañaga, E., Cutrale, F., Seriola', A., García-Díaz, M., Lagunas, A., Andilla, J., Loza-Alvarez, P., Samitier, J., Ojosnegros', S. and Martinez, E. Nanopatterns of surface-bound ephrinB1 produce multivalent ligand-receptor interactions that tune EphB2 receptor clustering. Nano Letters, 18 (1): 629-637 (2018).

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- Pérez, J., Dulay, S., Mir, M. and Samitier, J. Molecular architecture for DNA wiring. Biosensors and Bioelectronics, 121 54-61 (2018).

Lab technicians
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Visiting researcher
Valeria Rizzuto
José Marrugo

RESEARCH PROJECTS

NANOVAX Nanovacunas diseñadas para inmunoterapia antitumoral (2016-2018)
PI: **Josep Samitier** | *EuroNanoMed (ERA-Net)*

BIOBOT Engineered biological soft robots based on neuro-muscular junction control (2017-2018)
PI: **Josep Samitier** | *MINECO, Proyectos EXPLORA Ciencia / Tecnología*

MINDS Plataforma MIcrofluídica 3D de cultivo Neuronal compartimentada para el estudio de enfermedades neurológicas (2016-2018)
PI: **Josep Samitier** | *MINECO, Proyectos I+D Excelencia*

Advancecat Acceleradora pel desenvolupament de teràpies avançades
PI: **Josep Samitier** | *ACCIÓ / Smart Specialization funds (RIS3CAT)*

Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
PI: **Josep Samitier** | *Obra Social La Caixa*

Personalizing pediatric cancer treatment with kinome analyses, cell-based funcional assays and microfluidics (2017-2020)
PIs: **Josep Samitier** / **Joan Montero** | *Fundación CELLEX*

ISCHEMSURG Miniaturized electrochemical sensor for monitoring of free flap ischemia in post-surgery (2017-2018)
PI: **Mònica Mir** | *CaixaImpulse*

Desarrollar un sistema de asistencia robótica para medicina y cirugía fetal (2016-2019)
PI: **Josep Samitier** | *Fundación CELLEX*

Desarrollo de una nueva tecnología lab-on-a-chip para la detección y cuantificación de secuencias de ADN/ARN
PI: **Josep Samitier** | *Genómica S.A.U*

nanoET-leukemia Nanoconductance of electron transfer proteins of the respiratory chain. Direct measurement at the single molecular level and therapeutic regulation in cancer stem cells (2015-2018)
PIs: **Anna Lagunas** / **Marina Inés Giannotti** | *MINECO, Proyectos RETOS 2015 / CIBER*

MASCTN-Training Training on Advanced Stem Cell Technologies in Neurology
PI: **Josep Samitier** | *European Commission MARIE CURIE - ITN/813851*

SGR Grups de recerca consolidats 2017-2019
PI: **Josep Samitier** | *AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1079*

SGR Grups de recerca consolidats 2017-2019
PI: **Joan Montero** | MINECORYC-Ramon y Cajal/RYC-2015-18357

Urrea, L., Segura, M., Masuda-Suzukake, M., Hervera, A., Pedraz, L., Aznar, J. M. G., Vila, M., Samitier, J., Torrents, E., Ferrer, I., Gavín, R., Hagesawa, M. and Del Río, J. A. Involvement of cellular prion protein in ⍰-synuclein transport in neurons. Molecular Neurobiology, 55 (3): 1847-1860 (2018).

Marrugo-Ramírez, J., Mir, M. and Samitier, J. Blood-based cancer biomarkers in liquid biopsy: A promising non-invasive alternative to tissue biopsy. International Journal of Molecular Sciences, 19 (10): 2877 (2018).

Silva, N., Riveros, A., Yutronic, N., Lang, E., Chornik, B., Guerrero, S., Samitier, J., Jara, P. and Kogan, M. J. Photothermally controlled methotrexate release system using β-cyclodextrin and gold nanoparticles. Nanomaterials, 8 (12): 985 (2018).

García-Lizarribar, A., Fernández-Garibay, X., Velasco-Mallorquí, F., Castaño, A. G., Samitier, J. and Ramon-Azcon, J. Composite biomaterials as long-lasting scaffolds for 3D bioprinting of highly aligned muscle tissue. Macromolecular Bioscience, 18 (10): 1800167 (2018).

Páez-Avilés, C., Juanola-Feliu, E. and Samitier, J. Cross-fertilization of Key Enabling Technologies: An empirical study of nanotechnology-related projects

- Neuroblastoma en un chip para investigar la resistencia a fármacos y el uso de nanopartículas terapéuticas
PI: **Aranzazu Villasante** | *Asociación Española contra el Cáncer (AECC)*

- Personalizing Melanoma Treatment Using Dynamic BH3 Profiling
PI: **Joan Montero** | *Dana-Farber Cancer Institute, Inc. Dana-Farber Cancer Institute, Inc./6275103*

- Personalizing pediatric cancer treatment
PI: **Joan Montero** | *Fundación FERO Fundación de investigación Oncológica - FERO*

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based on innovation management strategies. Journal of Engineering and Technology Management, 49 22-45 (2018).

- Páez-Avilés, C., van Rijnsoever, F. J., Juanola-Feliu, E. and Samitier, J. Multi-disciplinarity breeds diversity: the influence of innovation project characteristics on diversity creation in nanotechnology. Journal of Technology Transfer, 43 (2): 458-481 (2018).

- Casanellas, I., Lagunas, A., Tsintzou, I., Vida, Y., Collado, D., Pérez-Inestrosa, E., Rodríguez-Pereira, C., Magalhaes, J., Gorostiza, P., Andrades, J. A., Becerra, J. and Samitier, J. Dendrimer-based uneven nanopatterns to locally control surface adhesiveness: A method to direct chondrogenic differentiation. Journal of Visualized Experiments, Bioengineering (131): e56347 (2018).

- Casanellas, I., García-Lizarribar, A., Lagunas, A. and Samitier, J. Producing 3D biomimetic nanomaterials for musculoskeletal system regeneration. Frontiers in Bioengineering and Biotechnology, 6 Article 128 (2018).

- Badiola-Mateos, M., Hervera, A., del Río, J. A. and Samitier, J. Challenges and future prospects on 3D in-vitro modeling of the neuromuscular circuit. Frontiers in Bioengineering and Biotechnology, 6 Article 194 (2018).

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Dr. Joan Lluis Vives Josep Carreras, Leukaemia Research Institute, Barcelona, Spain

Industry partners:
Biokit S.A. (Werfen group); Genomica S.A.U. (Zeltia group); Tallers Fiestas S.L.; Enantia S.L.; Microfluidic ChipShop GmbH; Minifab; Microliquid

EQUIPMENT AND TECHNIQUES

Nanofabrication and nanomanipulation
- 3D Printing system for microfluidic devices
- Graphtech

Characterization
- Potentiostates
- Optical Waveguide Lightmode Spectroscope (OWLS)
- Atomic Force Microscope (AFM)
- Optical Microscopes (white light/epifluorescence)
- Electrical Impedance spectroscopy (EIS)
- Multi-frequency Lock-in Amplifier
- Sub-femtoamp Remote SourceMeter Instrument

Molecular/cell biology
- Biological safety cabinet (class II)
- Microwell plate readers
- Protein and DNA electrophoresis systems
- Microincubator Okolab
- Nanodrop spectrophotometer
- CO2 incubator for cells: Galaxy® 48 S, 48 L, 230
- V/50/60 Hz, standard
- Cell culture cabin: Bioii-Advance 3

Microfluidics
- High precision syringe pumps
- Peristaltic pumps

Smart nano-bio-devices
Samuel Sánchez (ICREA Research Professor)

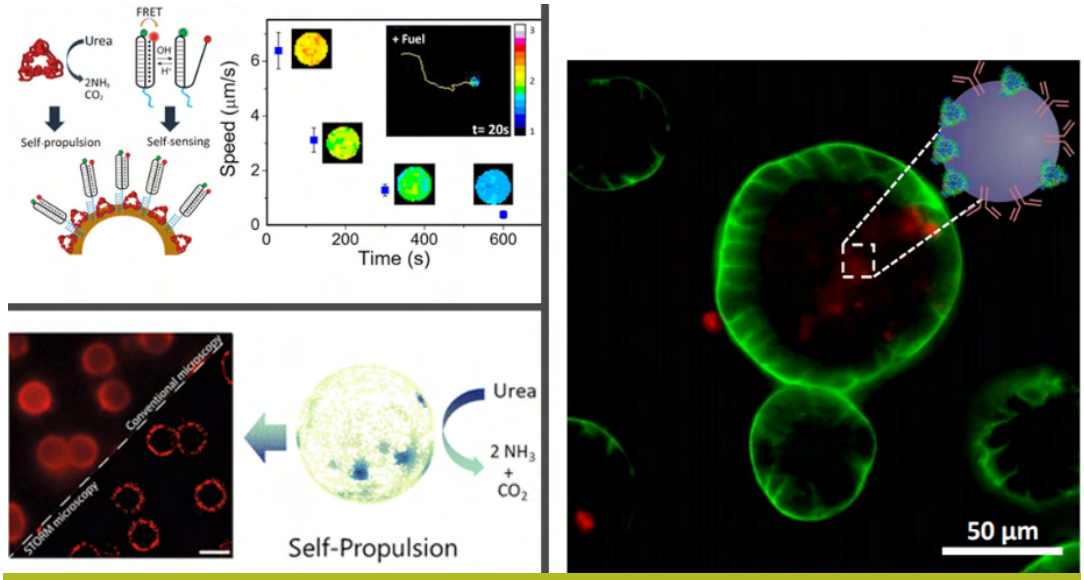
We develop different Systems ranging from active nanoparticles (nanobots), 3D Bioprinted Actuators and flexible biosensors. We are interested in fundamental studies of active matter, the use of nanobots for future nanomedicine and environmental applications and the bioengineering of new devices based on hybrid systems.

Nano-Bio Team

The use of enzyme catalysis is emerging as an attractive alternative to power micro- and nanomachines due to their unique features including biocompatibility, versatility and fuel bioavailability. Our group has demonstrated the use of different enzymes, including urease and glucose oxidase, to generate active propulsion of nano- and microparticles, paving the way towards new applications of artificial active matter in biomedicine. We have recently demonstrated that using enzyme-powered nanomotors can enhance anti-cancer drug delivery *in vitro*, improve the targeting of 3D bladder cancer spheroids and sense their surrounding environment. We are also interested in understanding the fundamental aspects underlying the motion of biocatalytic microswimmers for a safe and efficient design of micro- and nanomotors.

3D BioPrinted Soft Robotics

In the research line of soft bio-hybrid robotics, we explore the integration of biological tissue and artificial materials at larger length scales. In particular, we take advantage of the 3D bioprinting technique to develop bio-robotic systems composed of skeletal muscle cells embedded



Smart micro- and nanorobots are able to swim, monitor their own activity, sense their environment and deliver drugs to 3D bladder cancer spheroids using biocompatible and bioavailable fuels such as urea.

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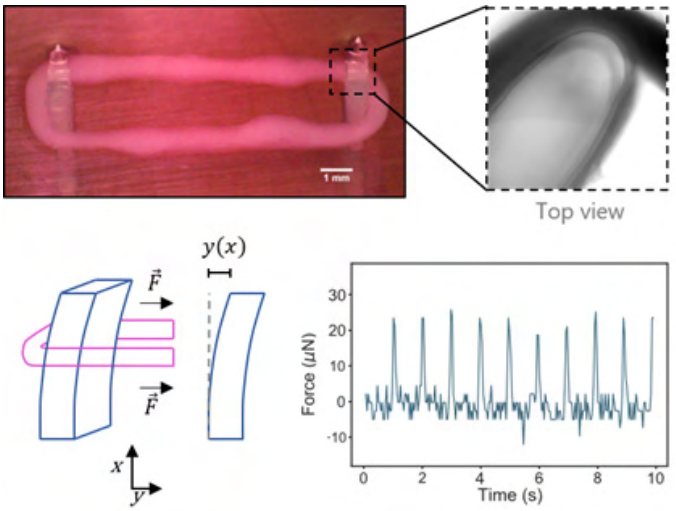
Joaquin Llacer
Guido Van Moolenbroek

Lab technician
Angel Blanco

in biocompatible hydrogels, which can be 3D bioprinted alongside other artificial materials. These materials can act as scaffolds, support, or flexible parts, as well as be responsive upon certain stimuli. By controlling the contractions of skeletal muscle cells *via* electric fields, we can measure the forces exerted by these bio-actuators against artificial 3D-printed posts. Using this setup, we have performed studies on the adaptability of bio-actuators after applying different training protocols and we have observed how their force generation and gene expression can adapt to the frequency of stimulation and stiffness of the artificial posts.

Active matter in complex systems

We study colloidal suspensions of Pt-coated silica particles as a model system of synthetic active matter. These systems have mostly been studied in homogeneous environments until now. Our interest lies in observing these systems in more complex settings, such as near interfaces, complex media or with flow involved. Since the self-propelled particles generate chemical and hydrodynamic fields around them, they interact in complex ways with flows and nearby surfaces that often leads to



3D-bioprinted bio-actuator based on skeletal muscle used as a force measurement platform. Upon electrical stimulation, the muscle can contract, bend the post and their force can be calculated.

PUBLICATIONS

Patiño, T., Arqué, X., Mestre, R., Palacios, L. and Sánchez, S. Fundamental aspects of enzyme-powered micro- and nanoswimmers. Accounts of Chemical Research, 51 (11): 2662–2671 (2018).

Patiño, T., Feiner-Gracia, N., Arqué, X., Miguel-López, A., Jannasch, A., Stumpp, T., Schäffer, E., Albertazzi, L. and Sánchez, S. Influence of enzyme quantity and distribution on the self-propulsion of non-Janus urease-powered micromotors. Journal of the American Chemical Society, 140 (25): 7896-7903 (2018).

Parmar, J., Vilela, D., Villa, K., Wang, J. and Sanchez, S. Micro- and nanomotors as active environmental microcleaners and sensors. Journal of the American Chemical Society, 140 (30): 9317-9331 (2018).

Vilela, D., Cossío, U., Parmar, J., Martínez-Villacorta, A. M., Gómez-Vallejo, V., Llop, J. and Sánchez, S. Medical imaging for the tracking of micromotors.

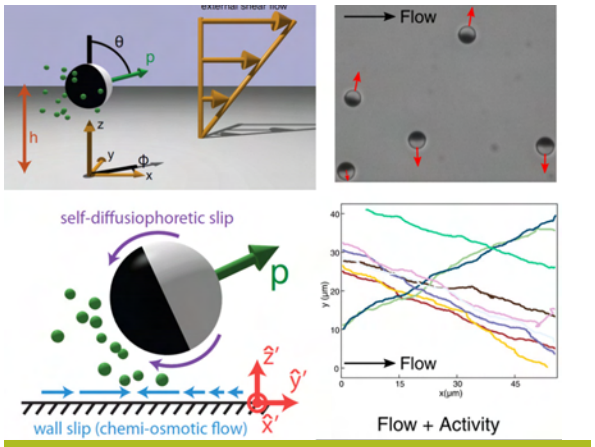
Smart nano-bio-devices

interesting behaviour. We could find, for instance, that close to solid surfaces they achieve a stable 'gliding' state which could be exploited to develop a system for guiding micro-nano motors using topographical features as shown with our micropatterned ratchets. When flow is present, particles also behave different as they reorient perpendicular to the flow.

Environmental applications of micro-nano motors

Artificial micromotors, based on bubble self-propulsion have demonstrated to be able to mix solutions and enhance chemical reactions while they swim. These micromotors are mostly based on two main structures, tubular and spherical.

First, we have designed tubular micromotors, which use hydrogen peroxide as a fuel, using different techniques such as, 'rolling-up' and electrodeposition. 'Rolling-up' microjets with a functional iron-based layer can generate and actively transport free radicals in the solution performing the degradation of organic dyes via Fenton-like reactions in presence of hydrogen peroxide. On the other hand, electrodeposited microjets, which are smaller



Catalytically active colloids generate chemical gradients and interact with their nearby surfaces while they swim. When they swim in capillaries where a flow is imposed, they present a cross stream migration deviating from straight trajectories, perpendicular to the flow lines. This type of motion resembles, in some aspects, the motion of biological microswimmers.

ACS Nano, 12 (2): 1120-1227 (2018).

Katuri, J., Caballero, D., Voituriez, R., Samitier, J. and Sanchez, S. Directed flow of micromotors through alignment interactions with micropatterned ratchets. ACS Nano, 12 (7): 7282-7291 (2018).

Wang, X., Sridhar, V., Guo, S., Talebi, N., Miguel-López, A., Hahn, K., van Aken, P. A. and Sánchez, S. Fuel-free nanocap-like motors actuated under visible light. Advanced Functional Materials, 28 (25): 1705862 (2018).

Hortelão, A. C., Patiño, T., Perez-Jiménez, A., Blanco, A. and Sánchez, S. Enzyme-powered nanobots enhance anticancer drug delivery. Advanced Functional Materials, 28 1705086 (2018).

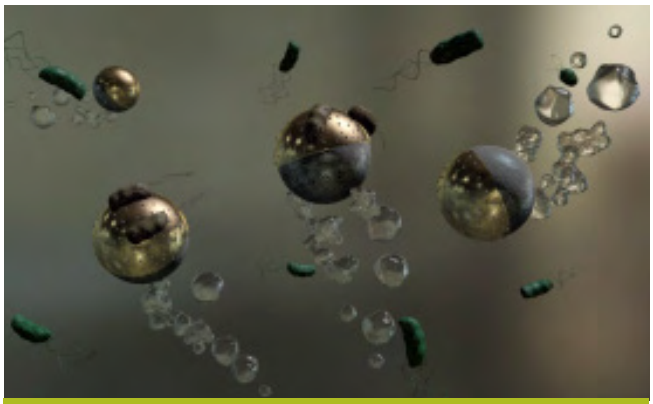
Xuan, M., Mestre, R., Gao, C., Zhou, C., He, Q. and Sánchez, S. Noncontinuous super-diffusive dynamics of a light-activated nanobottle motor. Angewandte Chemie International Edition, 57 (23): 6838-6842 (2018).

Katuri, J., Uspal, W. E., Simmchen, J., Miguel-López, A. and Sánchez, S. Cross-stream migration of active particles. Science Advances, 4 (1): eaao1755 (2018).

than their ‘roll-up’ counterparts, contain graphene-oxide on the outside working as ‘heavy metal scrubbers’. In this case, the metal is adsorbed and removed from the contaminated water. The metal can thereafter be desorbed and the microjets used again.

In order to target other water pollution problems, such as microorganism contamination, we have developed spherical microbots that can kill bacteria while they swim. These microbots have a Janus structure based on spherical magnesium microparticles, able to dissolve in water producing hydrogen bubbles, covered in one of their faces by Fe, Au and AgNPs which provide magnetic, bacteria attachment and bactericidal properties to the microjets.

Towards scaling-up of the micromotor synthesis for cleaning large volumes of water, we have fabricated micromotors using exclusively chemical methods such as, precipitation, reduction and sol-gel chemistry. These micromotors are based on a silica microtubular structure which contains an inner-layer of a catalytic material (PtNPs or MnO2) capable of removing pollutants efficiently from water while they swim in the presence of hydrogen peroxide. The external decoration of these structures with magnetic nanoparticles provides for good magnetic control. Finally, magnetic and catalytic micromotors formed by the aggregation of cobalt ferrite nanoparticles were synthesized to remove antibiotics from water. All these micromotors, due to their magnetic properties can be removed from the solution after finishing their targeting action by the application of an external magnetic field.



Micromotors can remove a wide variety of pollutants from contaminated water.

■ Villa, K., Parmar, J., Vilela, D. and Sánchez, S. Metal-oxide-based microjets for the simultaneous removal of organic pollutants and heavy metals. ACS Applied Materials & Interfaces, 10 (24): 20478-20486 (2018).

■ Villa, K., Parmar, J., Vilela, D. and Sanchez, S. Core-shell microspheres for the ultrafast degradation of estrogen hormone at neutral pH. RSC Advances, 8 (11): 5840-5847 (2018).

■ Romeo, A., Moya, A., Leung, T. S., Gabriel, G., Villa, R. and Sánchez, S. Inkjet printed flexible non-enzymatic glucose sensor for tear fluid analysis. Applied Materials Today, 10 133-141 (2018).

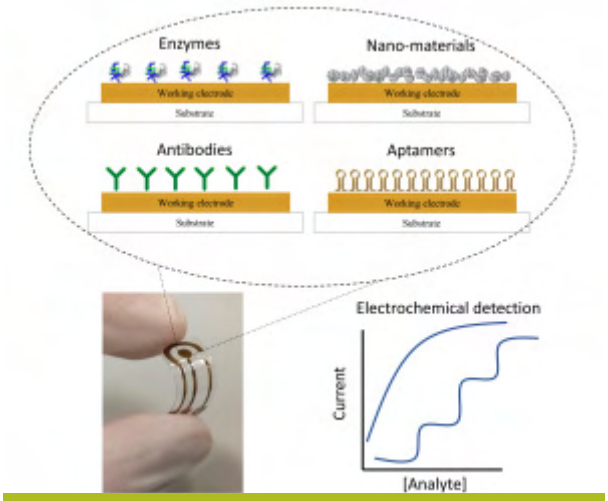
Conference Papers

■ Mestre, R., Patiño, T., Barceló, X. and Sanchez, S. 3D Bioprinted muscle-based bio-actuators: Force adaptability due to training. 7th International Conference, Living Machines 2018 (Lecture Notes in Computer Science). Paris, France (2018). Published by Springer International Publishing (2018/07/17).

Smart nano-bio-devices

(Flexible) Biosensors for non-invasive Point-of-Care diagnosticsv

Point-of-care diagnostics allows decentralizing clinical diagnostic practices and monitoring health out of specialized hospital settings. Advantages of such decentralization are improved quality of life of patients, enhanced therapeutic efficacy thanks to more frequent tests, and lower overall cost of the health system. We develop flexible biochemical sensors for non-invasive and cost-effective monitoring of analytes in biological fluids alternative to blood, e.g. sweat, tears, and saliva. We combine electrochemical electrochemical sensors with microfluidics and electronics to achieve fully integrated devices, that are well suited for low-cost, portable and user-friendly medical diagnostics.



Electrodes fabricated on flexible substrates are modified with a wide range of materials for selectivity towards biomarkers. Analytes are quickly quantified by electrochemical techniques.

RESEARCH PROJECTS

ENZWIM Nanomotores de nanopartículas mesoporosas impulsados por enzimas
PI: **Samuel Sánchez**
MINECO Explora Ciencia / Tecnología

MicroDia Sistemas Lab-on-a-chip basados en micro-nanomotores para el diagnóstico de enfermedades (2016-2018) | PI: **Samuel Sánchez** | *MINECO, Retos investigación: Proyectos I+D*

MICROCLEANERS Active microcleaners for water remediation (2016-2018) | PI: **Samuel Sánchez** | *European Research Council (ERC-PoC)*

LABPATCHLab-in-a-patch for PKU self-assessment | PI: **Samuel Sánchez** | E*uropean Commission ERC - PoC/790163*

LABPATCH SGR Grups de recerca consolidats 2017-2019 | PI: **Samuel Sánchez** | *AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1148*

MEDIROBOTS MEdical micro- and nano-Robots for Molecular Imaging | PI: **Samuel Sánchez** | *FBBVA Ayudas Fundación BBVA a Equipos de Investigación Científica*

COLLABORATIONS

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- **Dr. R. Artuch**, Laboratorio de enfermedades metabólicas hereditarias, Hospital Sant Joan de Déu, Barcelona. Spain

EQUIPMENT AND TECHNIQUES

- Autolab Galvostat/potentiostat (Metrohm)
- Dynamic light scattering (Wyatt)
- Langmuir Blodgett (KSV NIMA)
- Inverted Fluorescent microscope with cell incubator, galvo stage for 3D tracking (Leica DMi8); Inverted Fluorescent microscope (Leica DMI3000B); Upright microscope (Leica)
- Video camera (1000+ fps) (Hamamatsu)
- High speed camera (10000+ fps) (Vision Research)
- CCD video camera (100fps) (Thorlabs)
- Centrifuge (Eppendorf)
- UV- Visible spectrometer (Analytik Jena)
- 3D printer (Formlabs)
- Wave form source; Voltage amplifier (Tabor Electronics)
- DC power supply (Hameg)
- Oscilloscope (Rigol)
- Testtube heater; Eppendorf tube Shaker (Hach)
- Oxygen Plasma cleaner (Deiner Electronics)
- TOC Analyser (Analytik Jena)
- Spin coater (Laurell)
- High vacuum film deposition system (Leica Microsystems)
- UV irradiation system (Vilber Lourmat)
- Portable potentiostat-galvanostat and multiplexer (PalmSens)
- Sonicator (Branson)
- Thermolyne Furnace (Thermo Scientific)
- Hydrothermal Reactor (Berghof)
- Inkredible+ 3D Bioprinter (Cellink)
- Sonicator (VWR)
- DUO 3 Dual Stage Rotary Vane Vacuum Pump (Pfeiffer Vacuum)
- Orbital Shaker-Incubator ES-20 (Biosan)
- AL4000 Aladdin Double Syringe Pump (WPI)
- MFCS-EZ Microfluidic flow control system(Fluigent)

Bacterial Infections: Antimicrobial Therapies
Eduard Torrents

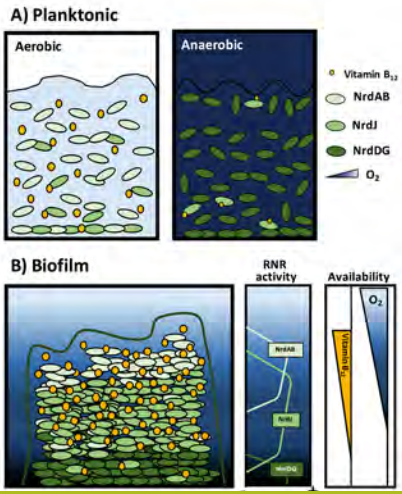
Infectious diseases constitute a tenacious and major public health problem all over the world. The emergence and increasing prevalence of bacterial strains that are resistant to available antibiotics demand the discovery of new therapeutic approaches.

There is an urgent need for reliable and rapid detection of infecting bacteria and its pattern of resistance to antibiotics.

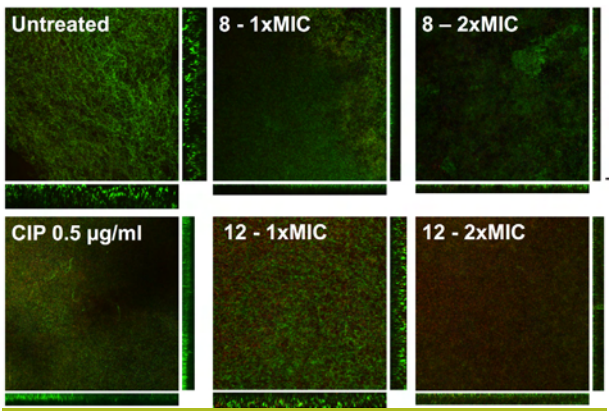
Our lab aims to investigate new antimicrobial therapies and strategies to combat bacterial infections with different objectives:

- to establish the molecular basis for the regulation of genes involved in DNA synthesis (ribonucleotide reductase genes), their importance in virulence and biofilm formation
- the identification and screening of new molecules for the highly selective inhibition of new antibacterial targets (e.g. ribonucleotide reductases)
- the use of nanomedicine techniques for the development of novel and specific nanoparticles to deliver existing antibiotics or new identify antimicrobial drugs, especially when the bacteria are growing in biofilm, close to the physiological conditions of the disease and where the current chemotherapy fails
- to study new methodologies to threat bacterial chronic infections in patients suffering cystic fibrosis
- to develop a new type of antibacterial vaccines
- the development of new strategies for bacterial co-culture systems
- to study and develop models for wound healing infections and the search of novel treatments
- the use of lab-on-a-chip technology to deeply elucidate mechanisms to combat bacterial forming biofilm as well as new approaches to identify multiresistant bacteria to different antibiotics

We believe these projects will be beneficial to society since we explore the use of different bioengineering approaches to elucidate ways to diagnose and eradicate multi-drug resistant bacteria.



Model of ribonucleotide reductase activity and vitamin B12 availability during P. aeruginosa planktonic and biofilm growth.



Antibacterial activity of two ribonucleotide reductase inhibitors on formed flow cell Pseudomonas aeruginosa biofilm.

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Maria Zimina
Núria Blanco
Lucas Pedraz
Aida Baelo

Masters student
Domingo Marchan

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Joan Ferrer
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RESEARCH PROJECTS

inhibitRNR Las ribonucleotido reductasas como una nueva diana terapéutica frente a patógenos bacterianos (2016-2019)
PI: **Eduard Torrents** | *MINECO, Retos investigación: Proyectos I+D*

Ribonucleotide reductasas: una nueva diana terapéutica contra organismos patógenos en enfermos de fibrosis quística (2010-2017)
PI: **Eduard Torrents** | *Asociación Española Fibrosis Quística/ PABLO MOTOS Becas de Investigación "Pablo Motos"*

Noves strategies antimicrobianes pel tractament de les enfermetats infeccioses en malalts de fibrosis quística
PI: **Eduard Torrents** | *La Caixa*

NBiofilmChip CaixaImpulse BiofilmChip
PI: **Eduard Torrents** | Obra Social La Caixa
Caixaimpluse

Fibrosi Quística Obra Social La Caixa
PI: **Eduard Torrents** | Obra Social La Caixa

COLLABORATIONS

Prof. Fernando Albericio, Institut de Recerca Biomèdica (IRB), Barcelona, Spain

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Dr. Joan Gavaldà, Infectious diseases, Vall d'Hebrón Hospital and Research Institute, Barcelona, Spain

Prof. Josep Samitier, Institute for Bioengineering of Catalonia (IBEC), (page 61)

Prof. Santiago Vazquez, Laboratori de química farmacèutica. Pharmacy Faculty, Barcelona University, Spain

Prof. Gabriel Gomilla, Institute for Bioengineering of Catalonia (IBEC), (page 21)

Prof. Vladimir Arion, Department of Inorganic Chemistry. University of Vienna, Austria.

Dr. Elena Martinez, Institute for Bioengineering of Catalonia (IBEC)

Dr. Luis Álvarez de Cienfuegos, Departamento de Química Orgánica. Facultad de Ciencias, Universidad de Granada, Spain

PUBLICATIONS

Urrea, L., Segura, M., Masuda-Suzukake, M., Hervera, A., Pedraz, L., Aznar, J. M. G., Vila, M., Samitier, J., Torrents, E., Ferrer, I., Gavín, R., Hagesawa, M. and Del Río, J. A. Involvement of cellular prion protein in α-synuclein transport in neurons. Molecular Neurobiology, 55 (3): 1847-1860 (2018).

Basas, J., Palau, M., Ratia, C., Luis Del Pozo, J., Martín-Gómez, M. T., Gomis, X., Torrents, E., Almirante, B. and Gavaldà, J. High-dose daptomycin is effective as an antibiotic-lock therapy in a rabbit model of Staphylococcus epidermidis catheter-related infection. Antimicrobial Agents and Chemotherapy, 62 (2): e01777 (2018).

Crespo, A., Blanco-Cabra, N. and Torrents, E. Aerobic vitamin B12 biosynthesis is essential for pseudomonas aeruginosa class II ribonucleotide reductase activity during planktonic and biofilm growth. Frontiers in Microbiology, 9 (986): Article 986 (2018).

Bacterial Infections: Antimicrobial Therapies

Prof. Luis Serrano i **Maria Lluch** del Centre de Regulacio Genòmica (CRG), Barcelona, Spain

EQUIPMENT AND TECHNIQUES

- Zeiss LSM 800 Confocal Laser Scanning Microscope Nikon Inverted Fluorescent microscope ECLIPSE Ti-S/ L100
- Spark® multimode microplate reader (TECAN)- anaerobic control / humidity cassette
- Cell culture facilities for microbial infections
- Biological safety cabinet (class II)
- Characterization of nanoparticles/biomaterial antibacterial activity
- Drosophila melanogaster and Galleria mellonella as a model host for bacterial infections
- Continuous flow system model for bacterial biofilm development
- Single Channel Fiber-Optic Oxygen Meter with microsensor
- Gradient thermocycler (PCR)
- Molecular biology facilities
- Protein and DNA electrophoresis
- Bacterial expression systems for heterologous protein production
- Protein purification systems (FPLC; Biologic DuoFlow System; Bio-Rad)
- Technology of microbial culture facilities.
- Pressure microinjection system
- Nikon Inverted fluorescent

- Pujol, E., Blanco-Cabra, N., Julián, E., Leiva, R., Torrents, E. and Vázquez, S. Pentafluorosulfanyl-containing triclocarban analogs with potent antimicrobial activity. Molecules, 23 (11): 2853 (2018).
- Miret-Casals, L., Baelo, A., Julián, E., Astola, J., Lobo-Ruiz, A., Albericio, F. and Torrents, E. Hydroxylamine derivatives as a new paradigm in the search of antibacterial agents. ACS Omega, 3 (12): 17057-17069 (2018).
- Lozano, H., Fabegas, R., Blanco-Cabra, N., Millán-Solsona, R., Torrents, E., Fumagalli, L., Gomila, G. Dielectric constant of flagellin proteins measured by scanning dielectric microscopy. Nanoscale. 10: 19188-19194 (2018).

Integrative cell and tissue dynamics
Xavier Trepat (ICREA Research Professor)

We aim at understanding how physical forces and molecular control modules cooperate to drive biological function.

We develop new technologies to map and perturb the main physical properties that determine how cells and tissues grow, move, invade and remodel. By combining this physical information with systematic molecular perturbations and computational models we explore the principles that govern the interplay between chemical and physical cues in living tissues.

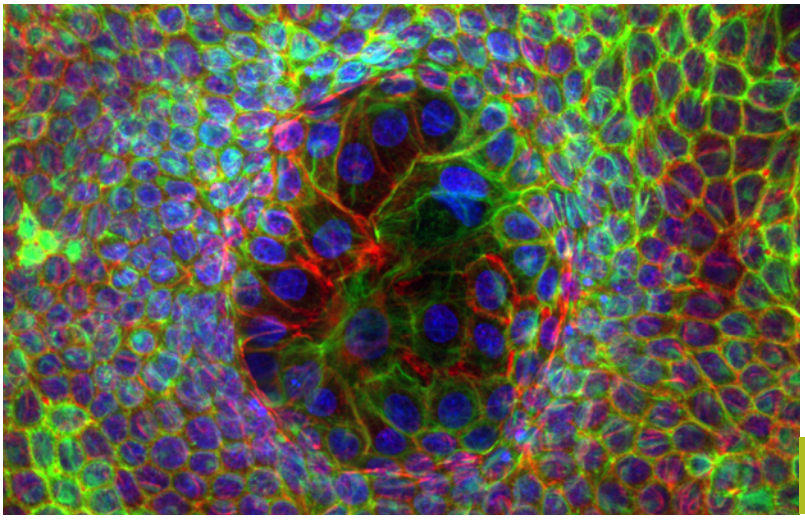
We study how these principles are regulated in physiology and development, and how they are derailed in cancer and aging.

Making cellular forces visible

To study cell and tissue dynamics we develop new technologies to measure physical forces at the cell-cell and cell-matrix interface. By combining these technologies with computational analysis of cell shape and velocity we obtain a full experimental characterization of epithelial dynamics during tissue growth, wound healing and cancer cell invasion.

Tumour invasion by stromal forces

Cancer cell invasion and metastasis remain the leading cause of death in patients with cancer. Both processes are the result of a complex interaction between tumor cells and their microenvironment. One of our main lines of research is to study how tumours exploit the functions non-cancer cells in their microenvironment to invade and metasize. We focus on the interaction between epithelial cancer cells and Cancer Associated Fibroblasts (CAFs), the most abundant cell type in the tumour stroma. In a recent study we were able to demonstrate that CAFs guide the collective invasion of cancer cells through a physical force. This force enables CAFs to physically drag cancer cells into the surrounding tissue. Force transmission is mediated by a heterotypic interaction between two different proteins, one located on the surface of cancer cells called E-cadherin, and another expressed on the surface of fibroblasts, called N-cadherin.



Super-stretched cells surrounded by only slightly deformed ones. The cell nucleus is shown in blue, actin filaments in red, and keratin filaments in green.

Integrative cell and tissue dynamics

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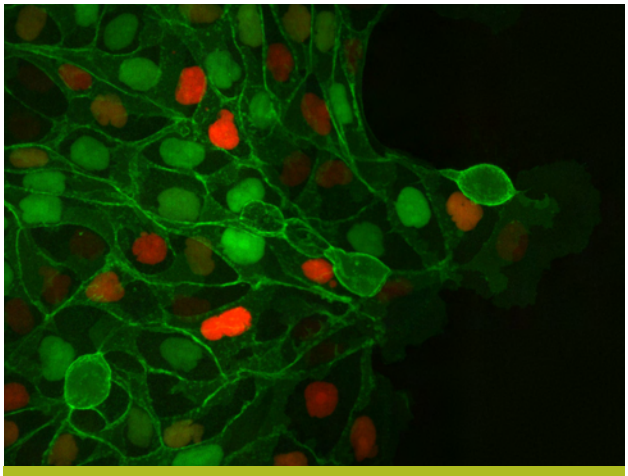
Visiting researchers
Jonel Trebicka

Optogenetics to control cell mechanics

The recent development of optogenetic technologies offers promising possibilities to control signalling pathways with high spatiotemporal resolution. By expressing genetically encoded light-sensitive proteins, optogenetic technology enables the reversible perturbation of intracellular biochemistry with subcellular resolution. We have developed optogenetic tools based on controlling the activity of endogenous RhoA to upregulate or downregulate cell contractility. We have shown that these tools enable rapid, local and reversible changes in traction forces, cell–cell forces, and tissue compaction. We have shown, that changes in cellular forces are paralleled by translocation of the transcriptional regulator YAP, indicating that our tools can be used to control mechanotransductory pathways.



An epithelium of cells of the MDCK line with the marked nuclei: the color ranges from red to green depending on the hase of the cell cycle; red for phase G1, green for phases S, G2 and M.

Collective durotaxis: a mechanism for cellular guidance by mechanical cues

Directed cell migration is one of the earliest observations in cell biology, dating back to the late XIX century. Also known as taxis, directed cell migration has been commonly associated with chemotaxis, i.e. the ability of a broad variety of cell types to migrate following gradients of chemical factors. We recently demonstrated a new mode of collective cell guidance by mechanical cues, called collective durotaxis. This new migration mode emerges only in cell collectives and, strikingly, does not require isolated cells to exhibit gradient sensing. To study the mechanisms behind this phenomenon, we developed new tools to measure the forces that propel cells during durotaxis at the cell-matrix and cell-cell levels. Upon combining this new experimental technique with biochemical approaches and theoretical modelling, we concluded that collective durotaxis originates from long-range transmission of contractile intercellular forces. This mechanism is unique in that the very same machinery that senses the attractant -the actomyosin cytoskeleton- is responsible for propulsion towards it. As such, collective durotaxis appears to be the simplest and perhaps most primitive mechanism by which a collective system responds to a gradient.

Microfabrication and wound healing

Using microfabrication technologies, we designed new ways to decipher the mechanisms of wound healing. By doing so we uncovered a new understanding of how cells move and work together to close a gap in a tissue. We showed that a new mechanism applies in which cells assemble supracellular contractile arcs that compress the tissue under the wound.

PUBLICATIONS

■ Shellard, A., Szabó, A., Trepat, X. and Mayor, R. Supracellular contraction at the rear of neural crest cell groups drives collective chemotaxis. Science, 362 (6412): 339-343 (2018).

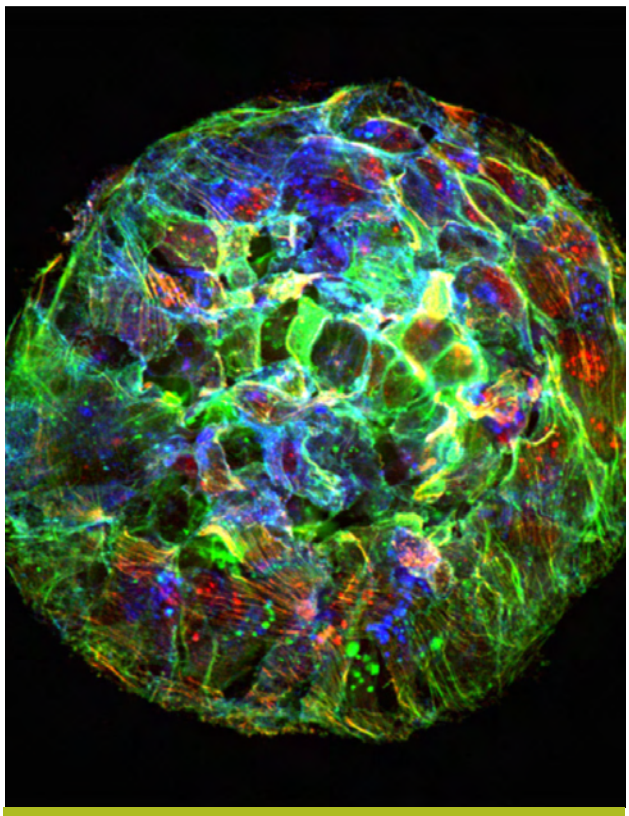
■ Latorre, E., Kale, S., Casares, L., Gómez-González, M., Uroz, M., Valon, L., Nair, R. V., Garreta, E., Montserrat, N., del Campo, A., Ladoux, B., Arroyo, M. and Trepat, X. Active superelasticity in three-dimensional epithelia of controlled shape. Nature, 563 (7730): 203-208 (2018).

■ Good, M. and Trepat, X. Cell parts to complex processes, from the bottom up. Nature, 563 (7730): 188-189 (2018).

■ Trepat, X. and Sahai, E. Mesoscale physical principles of collective cell organization. Nature Physics, 14 (7): 671-682 (2018).

■ Uroz, M., Wistorf, S., Serra-Picamal, X., Conte, V., Sales-Pardo, M., Roca-Cusachs, P., Guimerà, R. and Trepat, X. Regulation of cell cycle progression by

By combining experiments and computational modeling, we showed that contractions arising from these arcs make the wound heal in a quicker and more robust way.



Breast cancer cells attached to a surface rich in collagen. The actin cytoskeleton can be seen in green, coated with active myosin (ppMLC) in red, and the cell-cell junctions (E-cadherin) in blue.

Stretching epithelial tissues

Epithelial tissues are fundamental to life, as they protect the body from radiation, pollutants and pathogens. They're also responsible for gas exchange in the lungs, absorption of nutrients in the gut, and excretion of urine in the kidneys. We developed a new approach to subject epithelial tissues to very large deformations, up to four times their original size. Most materials are 'unhappy' during stretching. As they become progressively deformed, they want to go back to their unstretched state, like a rubber band, or may even break as the tension increases. We found that epithelial sheets have a different and unusual mechanical behavior. To our surprise, tissues did not break during stretching, and they were able to recover their initial size in a fully reversible way when unstretched. Even more surprisingly, some cells in the tissue barely stretched, while others became 'superstretched', increasing their area more than ten times. We identified the molecular mechanisms that explain this physical behavior, which we call 'active superelasticity' as an analogy with the behavior of some high-tech metal alloys used in medical technologies. Understanding this surprising mechanical behavior in epithelial tissues could help us build better artificial organs or new bionic technologies such as organs-on-a-chip.

cell–cell and cell–matrix forces. Nature Cell Biology, 20 (6): 646-654 (2018).

■ Elosegui-Artola, A., Trepat, X. and Roca-Cusachs, P. Control of mechanotransduction by molecular clutch dynamics. Trends in Cell Biology, 28 (5): 356-367 (2018).

■ Thottacherry, J. J., Kosmalska, A. J., Elosegui-Artola, A., Pradhan, S., Sharma, S., Singh, P. P., Guadamillas, M. C., Chaudhary, N., Vishwakarma, R., Trepat, X., del Pozo, M. A., Parton, R. G., Pullarkat, P., Roca-Cusachs, P. and Mayor, S. Mechanochemical feedback and control of endocytosis and membrane tension. Nature Communications, 9 4217 (2018).

■ Labernadie, A. and Trepat, X. Sticking, steering, squeezing and shearing: cell movements driven by heterotypic mechanical forces. Current Opinion in Cell Biology, 54 57-65 (2018).

■ Pardo-Pastor, C., Rubio-Moscardo, F., Vogel-González, M., Serra, S. A., Afthinos, A., Mrkonjic, S., Destaing, O., Abenza, J. F., Fernández-Fernández, J. M., Trepat, X., Albiges-Rizo, C., Konstantopoulos, K. and Valverde, M. A. Piezo2 channel regulates RhoA and actin cytoskeleton to promote cell mechanobiological

Integrative cell and tissue dynamics

RESEARCH PROJECTS

DUROTAXIS Mecanobiología de la durotaxis: de las células aisladas a los tejidos
PI: **Xavier Trepat**
MINECO Proyectos I+D Excelencia/BFU2015-65074-P

TENSIONCONTROL Multiscale regulation of epithelial tension (2015-2019)
PI: **Xavier Trepat**
European Research Council - CoG

Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biòpsies
PI: **Josep Samitier**
Obra Social La Caixa

MECHANO-CONTROL Mechanical control of biological function
PI: **Pere Roca-Cusachs**
European Commission. FET Proactive/731957

MECHADIAN Mechanobiology of the cellular circadian clock
PI: **Juan Francisco Abenza**
European Commission. MARIE CURIE - IF/750557

SGR Grups de recerca consolidats 2017-2019
PI: **Xavier Trepat**
AGAUR. SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1602

SGR Grups de recerca consolidats 2017-2019
PI: **Anna Labernadie**
Obra Social La Caixa. Junior Leader Program

COLLABORATIONS

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Erik Sahai, Cancer Research, UK

Benoit Ladoux, Université Paris 7, France

Jim Butler and **Jeff Fredberg**, Harvard University, Boston, USA

Danijela Vignjevic, Institut Curie, Paris, France

Arancha del Campo, Leibniz-Institut für Neue Materialien, Saarbrücken

responses. Proceedings of the National Academy of Sciences of the United States of America, 115 (8): 1925-1930 (2018).

Dix, C. L., Matthews, H. K., Uroz, M., McLaren, S., Wolf, L., Heatley, N., Win, Z., Almada, P., Henriques, R., Boutros, M., Trepat, X. and Baum, B. The role of mitotic cell-substrate adhesion re-modeling in animal cell division. Developmental Cell, 45 (1): 132-145 (2018).

De Pascalis, C., Pérez-González, C., Seetharaman, S., Boëda, B., Vianay, B., Burute, M., Leduc, C., Borghi, N., Trepat, X. and Etienne-Manneville, S. Intermediate filaments control collective migration by restricting traction forces and sustaining cell–cell contacts. The Journal of Cell Biology, 217 (9): 3031-3044 (2018).

Kuipers, A. J., Middelbeek, J., Vrenken, K., Pérez-González, C., Poelmans, G., Klarenbeek, J., Jalink, K., Trepat, X. and van Leeuwen, F. N. TRPM7 controls mesenchymal features of breast cancer cells by tensional regulation of SOX4. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1864 (7): 2409-2419 (2018).

SCIENTIFIC EQUIPMENT AND TECHNIQUES

- Soft Lithography
- Micro/Nano Fabrication
- Cell stretching
- Live Confocal Microcopy
- Magnetic Tweezers
- Magnetic Twisting Cytometry
- Monolayer stress microscopy
- Traction Microscopy

- Sehgal, P., Kong, X., Wu, J., Sunyer, R., Trepat, X. and Leckband, D. Epidermal growth factor receptor and integrins control force-dependent vinculin recruitment to E-cadherin junctions. Journal of Cell Science, 131 (6): jcs206656 (2018).
- Escribano, J., Sunyer, R., Sánchez, M. T., Trepat, X., Roca-Cusachs, P. and García-Aznar, J. M. A hybrid computational model for collective cell durotaxis. Biomechanics and Modeling in Mechanobiology, 17 (4): 1037-1052 (2018).

Synthetic, Perceptive, Emotive and Cognitive Systems (SPECS)
Paul Verschure (ICREA Research Professor)

SPECS uses synthetic methods to study and synthesize the neuronal, psychological and behavioural principles underlying perception, emotion, and cognition

SPECS activities are organized around several complementary dimensions:

- Architectures of mind and brain
- Cognitive, Motor, Sensory learning systems
- Embodied Autonomous systems
- Real time Interaction technology
- Neurorehabilitation

SPECS is also very much involved in the development of scientific co-operations in the field of Biomimetics and Neurotechnology, as well as in Educational and Outreach activities.

Computational & Cognitive Systems

The Cognitive Systems Laboratory is a multidisciplinary environment that supports research on detailed biologically grounded models of the cerebellum, hippocampus, and cortex which all have directly fed into the system level models tested in the in the following areas:

- Distributed Adaptive Control underlying the Mind, Brain, Body Nexus (MBBN)
- Multi-agents exploration and coordination
- Classical conditioning, operant conditioning and learning models based on the Distributed Adaptive Control framework, which has become a standard in the field of artificial intelligence and behavior-based robotics.

The eXperience Induction Machine (XIM) with the interactive application BrainX3.

Senior researcher
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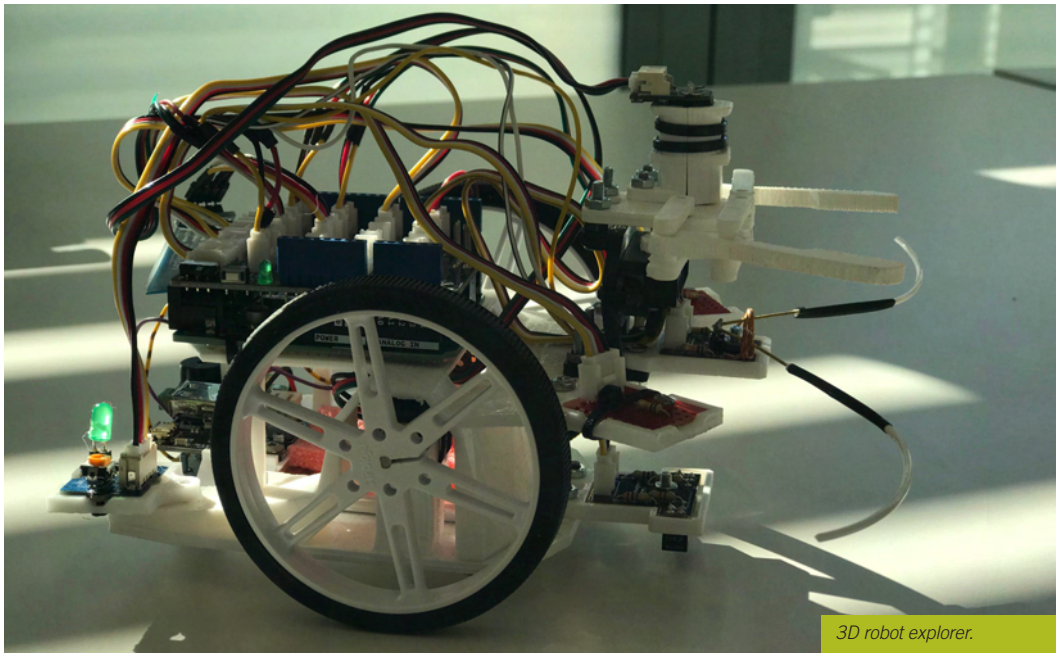
Robotic Systems

The Robotic Systems Laboratory is a multidisciplinary environment that supports research in the following areas:

- Classical conditioning, operant conditioning and learning models based on the Distributed Adaptive Control framework, which has become a standard in the field of artificial intelligence and behavior-based robotics
- Multi-robot exploration and coordination
- Navigation in human and animal behavior
- Implementation in robots of brain models of the hippocampus, cerebellum, thalamus/cortex
- Rule learning VR robots/avatars
- Fast and reliable insect-based visual navigation models for flying vehicles Investigation of the neuronal substrates of chemical sensing and their application to odor discrimination and localization.



3D robot explorer.

PUBLICATIONS

- Munoz, J. J., Amat, D. and Conte, V. Computation of forces from deformed visco-elastic biological tissues. Inverse Problems, 34 (4): 044001 (2018).
- Zamora, R., Korff, S., Mi, Q., Barclay, D., Schimunek, L., Zucca, R., Arsiwalla, X. D., Simmons, R. L., Verschure, P., Billiar, T. R. and Vodovotz, Y. A computational analysis of dynamic, multi-organ inflammatory crosstalk induced by endotoxin in mice. PLoS Computational Biology, 14 (11): e1006582 (2018).
- Arsiwalla, X. D. and Verschure, P. Measuring the complexity of consciousness. Frontiers in Neuroscience, 12 (424): Article 424 (2018).
- Santos-Pata, D. and Verschure, P. Human vicarious trial and error is predictive of spatial navigation performance. Frontiers in Behavioral Neuroscience, 12 Article 237 (2018).
- Truschzinski, M., Betella, A., Brunnett, G. and Verschure, P. Emotional and cognitive influences in air traffic controller

Synthetic, Perceptive, Emotive and Cognitive Systems (SPECS)

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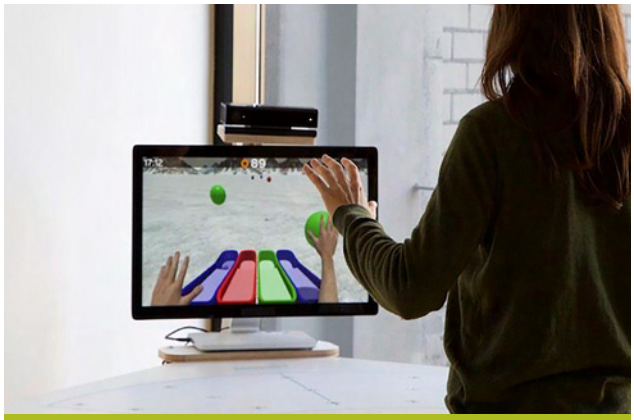
Neurorehabilitation

Over the past 15 years, SPECS has been developing science-based technology tools to drive perceptual, cognitive, affective and motor systems of the brain to facilitate functional recovery after damage. By means of novel interaction paradigms such as Virtual Reality or music therapy, and based on the Distributed Adaptive Control theory of mind and brain DAC developed by Paul Verschure, SPECS studies the brain and the mechanisms underlying loss of function and its rehabilitation and recovery after stroke, and other brain diseases (see Verschure Conf Proc IEEE Eng Med Biol Soc. 2011, Mónica S. Cameirão et al. Restor Neurol Neurosci 2011 and Stroke 2012)



Rgs Full Body.

Neuropsychophysiology lab

The Psychophysiology lab studies how humans react to various uni- and multisensory signals – visual, auditory and tactile stimuli. We assess human responses at different levels using subjective ratings, behavioral data, physiological and brain wave recordings. This data helps us to understand human perception and cognition mechanisms, with particular stress on the novel methods for diagnosis and treatment of various brain disorders (chronic pain, migraine, autism, depression, Alzheimer's disease).

- Affective chronometry (such parameters as the rise time to peak and the recovery time of the emotional waveform)
- Multisensory perception (sound, vision, touch)
- Multisensory interactions for emotional stimuli (custom sound and video databases are created)
- Sonification of EEG signals
- Neurofeedback using mixed reality environments processing of eye-gaze in autistic children

Hybrid Systems laboratory (HLB)

The HLB is primarily involved in the development, implementation, and analysis of machine-brain-machine interfaces. The HLB was involved in the ReNaChip FP7 project, whose overarching goal is to build neuroprosthetic

tasks: An investigation using a virtual environment? Applied Ergonomics, 69 1-9 (2018).

- Pacheco, D. and Verschure, P. F. M. J. Long-term spatial clustering in free recall. Memory, 26 (6): 798–806 (2018).

- Blancas-Muñoz, M., Vouloutsi, V., Zucca, R., Mura, A. and Verschure, P. Hints vs distractions in intelligent tutoring systems: Looking for the proper type of help. ARXIV, Computer Science (Human-Computer Interaction): 1-4 (2018).

- Freire, I. T., Moulin-Frier, C., Sanchez-Fibla, M., Arsiwalla, X. D. and Verschure, P. Modeling the formation of social conventions in multi-agent populations. ARXIV, Computer Science (Multiagent Systems): 1-30 (2018).

- Fischer, T., Puigbò, J.-Y., Camilleri, D., Nguyen, P. D. H., Moulin-Frier, C., Lallée, S., Metta, G., Prescott, T. J., Demiris, Y. and Verschure, P. iCub-HRI: A software framework for complex human-robot interaction scenarios on the iCub humanoid robot. Frontiers in Robotics and AI, 5 (22): Article 22 (2018).

- Moulin-Frier, C., Fischer, T., Petit, M., Pointeau, G., Puigbo, J., Pattacini, U., Low, S. C., Camilleri, D., Nguyen, P., Hoffmann, M., Chang, H. J., Zambelli, M., Mealier, A., Damianou, A., Metta, G., Prescott, T. J., Demiris, Y., Dominey, P. F. and Verschure, P. F. M. J. DAC-h3: A proactive robot cognitive architecture to acquire and express knowledge about the world and the self. IEEE Transactions on Cognitive and Developmental Systems, Early Access (2018).

Conference paper

- Arsiwalla, X., Signorelli, C. M., Puigbo, J.-Y., Freire, I. and Verschure, P. Are brains computers, emulators or simulators? 7th International Conference, Living Machines 2018 (Lecture Notes in Computer Science). Paris, France (2018). Published

neuromorphic chip recovering a learning function lost in the aged cerebellum. The interdisciplinary nature of the study of hybrid systems lies at the intersection of different research areas, namely:

- Computational neuroscience
- Electronics
- Robotics
- Artificial intelligence
- Neuromorphic engineering

Digital Heritage

By using advanced digital humanities technologies, and making it accessible online, we can conserve, develop and preserve the memory of Europe's cultural heritage, and in particular the Holocaust, for future generations.

Existing memorial sites or museums offer a traditional historiographical approach. We propose to use virtual and augmented reality techniques to reconstruct sites of World War-II crimes and their interrelated structures. SPECS's approach combines virtual and augmented reality with integrated databases of graphical reconstructions and historical sources to allow us to actively explore and try to comprehend the incomprehensible: the massive scale of the crimes Nazi Germany perpetrated on the world and the depth of the destruction and suffering it caused.

The SPECS research group has been pioneering this approach over the last 15 years and grounded it in its fundamental research in psychology and neuroscience. In collaboration with the Bergen-Belsen memorial site and Prof. Habbo Knoch, this paradigm has been elaborated to conserve and present the history of the Bergen Belsen concentration camp.

Educational Robotics

Technology evolves and advances faster than ever in all aspects of our society. Thus, it is important that the next generations of students learn as much as possible about emerging technology and stay competitive.

SPECS contributes to the education of the next generations by combining platforms for training and outreach activities, facilitating multidisciplinary education and innovation by sharing the value of convergent science, excellence, and societal impact. We have developed Educational Robotics programs for students of the primary and secondary school, as well as courses to train teachers and young adults.

Interaction Technology

There is a growing interest in understanding creativity from a more neuroscientific point of view, so to say, to disclose the neural basis of creativity we will need great insights on how the brain elaborates the process of human thought.

by Springer International Publishing (2018/07/17).

- Freire, I., Puigbo, J., Arsiwalla, X. and Verschure, P. Modeling the opponent's action using control-based reinforcement learning. 7th International Conference, Living Machines 2018 (Lecture Notes in Computer Science). Paris, France (2018). Published by Springer International Publishing (2018/07/17).

- Puigbò, J. Y., Arsiwalla, X. D. and Verschure, P. Challenges of machine learning for living machines. 7th

- International Conference, Living Machines 2018 (Lecture Notes in Computer Science). Paris, France (2018). Published by Springer International Publishing (2018/07/17).

- Santos-Pata, D., Escuredo, A., Mathews, Z. and Verschure, P. Insect behavioral evidence of spatial memories during environmental reconfiguration. 7th International Conference, Living Machines 2018 (Lecture Notes in Computer Science). Paris, France (2018). Published by Springer International Publishing (2018/07/17).

- Arsiwalla, X. D., Pacheco, D., Principe, A., Rocamora, R. and Verschure, P. A temporal estimate of integrated information for intracranial functional connectivity. 27th International Conference on Artificial Neural Networks (ICANN 2018). Rhodes, Greece (2018). Published by Springer, Cham (2018/10/04).

- Maier, M., Low, S. C., Ballester, B. R., Bañuelos, N. L., Oller, E. D. and Verschure, P. Depression modulates attentional processing after stroke. 4th International Conference on NeuroRehabilitation (ICNR2018). Pisa, Italy (2018). Published by Springer, Cham (2018/10/16).

- Moulin-Frier, C., Puigbò, J. Y., Arsiwalla, X. D., Sanchez-Fibla, M. and Verschure, P. Embodied artificial intelligence through distributed adaptive control: An integrated

Synthetic, Perceptive, Emotive and Cognitive Systems (SPECS)

Our approach to understanding the process of creativity is to use Art & Technology to create high impact, sophisticated man-machine interaction tools.

- Narrative in interactive mixed reality environment
- Multimedia installations: affect-based self-generated media content

Interaction Technology

There is a growing interest in understanding creativity from a more neuroscientific point of view, so to say, to disclose the neural basis of creativity we will need great insights on how the brain elaborates the process of human thought.

Our approach to understanding the process of creativity is to use Art & Technology to create high impact, sophisticated man-machine interaction tools.

- Narrative in interactive mixed reality environment
- Multimedia installations: affect-based self-generated media content

Mixed-reality lab

The Mixed-reality lab serves a threefold research agenda:

- Understand human behavior in a mixed-reality context
- Build mixed-reality applications based on neurobiological understanding and methodologies such as the BrainX3
- Test neurobiological models by deploying them in control of mixed-reality systems

RESEARCH PROJECTS

DAC-CHM Control Adaptable Distribuido de la conciencia en humanos y máquinas | PI: **Paul Verschure** | *MINECO Retos investigación: Proyectos I+D/PSI2016-79968-P*

iC-ACCESS Accessing Campscapes: Inclusive Strategies for Using European Conflicted Heritages | PI: **Paul Verschure** | *HERA Humanities in the European Research area/78581*

CDAC The role of consciousness in adaptive behavior: A combined empirical, computational and robot based approachs | PI: **Paul Verschure** | *European Commission ERC - AdG/341196*

ANITA Advanced tools for fighting oNline Illegal TrAffickings | PI: **Paul Verschure** | *European Commission Research and Innovation action/787061*

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Book

- Prescott, T. J., Lepora, N. and Verschure, P. Living machines: A handbook of research in biomimetics and biohybrid systems. (ed. Oxford, UK. Oxford Scholarship (2018).
- Vouloutsi, V., Halloy, J., Mura, A., Mangan, M., Lepora, N., Prescott, T. J. and Verschure, P. Biomimetic and Biohybrid Systems. (ed. Lausanne, Switzerland. Springer International Publishing (2018).

Book chapter

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- Pfeifer, R. and Verschure, P. The challenge of autonomous agents: Pitfalls and how to avoid them. In: The Artificial Life Route to Artificial Intelligence (ed. Steels, L. and Brooks, R.). New York, USA, Taylor & Francis Group. 9: 237-266 (2018).
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VirtualBrainCloud Personalized Recommendations for Neurodegenerative Diseases | PI: **Paul Verschure** | *European Commission Digital transformation in Health and Care/826421*

HR-Recycler Hybrid Human-Robot RECYcling plant for electriCal and eLEctRonic equipments | PI: **Paul Verschure** | *European Commissions | Transforming European Industry/820742*

socSMCs Socialising Sensori-Motor Contingenciess | PI: **Paul Verschure** | *European Commission FET Proactive/641321*

SGR Grups de recerca consolidats 2017-2019s | PI: **Paul Verschure** | *AGAUR SGR-Ajuts per donar suport a les activitats dels grups de recerca de Catalunya/2017 SGR 1675*

Pla de creixement del grup de recerca SPECS PI: **Paul Verschure** | *ACCIO. Ajuts per l'execució dels plans d'actuació en transferència tecnològica dels desenvolupadors públics de tecnologia candidats a ser acreditats TECNIO/TECDTP16-1-0016-00*

Research agreement on human-autonomy systems PI: **Paul Verschure** | *DCS Corporation*

EQUIPMENT AND TECHNIQUES

The eXperience Induction Machine (XIM), an immersive space equipped with a number of sensors and effectors that have been constructed to conduct experiments in mixed-reality.

Robotics lab

Codi-Bot, the musical robot that teaches you how to program

Collective machine cognition: Autonomous dynamic mapping and planning using a hybrid team of aerial and ground-based robots

Robots: Humanoids Pepper, iCub and 3D printed robots, Drones

Rehabilitation Gaming Systems

BrainX3

Digital applications for Cultural heritage

Living machines: A handbook of research in biomimetics and biohybrid systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 239-255 (2018).

Lepora, N., Verschure, P. and Prescott, T. J. A roadmap for Living Machines research. In: Living machines: A handbook of research in biomimetics and biohybrid systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 26-50 (2018).

Prescott, T. J. and Verschure, P. F. M. J. Living machines: An introduction. In: Living Machines: A Handbook of Research in Biomimetic and Biohybrid Systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 3-14 (2018).

Verschure, P. The architecture of mind and brain. In: Living machines: A handbook of research in biomimetics and biohybrid systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 338-345 (2018).

Verschure, P. A chronology of Distributed Adaptive Control. In: Living machines: A handbook of research in biomimetics and biohybrid systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 346-360 (2018).

Verschure, P. Capabilities. In: Living machines: A handbook of research in biomimetics and biohybrid systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 211-217 (2018).

Verschure, P. and Prescott, T. J. A living machines approach to the sciences of mind and brain. In: Living Machines: A Handbook of Research in Biomimetic and Biohybrid Systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 15-25 (2018).

Vouloutsi, V. and Verschure, P. Emotions and self-regulation. In: Living Machines: A Handbook of Research in Biomimetic and Biohybrid Systems (ed. Prescott, T. J., Lepora, N. and Verschure, P.). Oxford, UK, Oxford Scholarship: 327-337 (2018).

OPENLAB

Open Innovation Lab

Direct towards the patient and the market: The Open Innovation Lab for Bioengineering is an IBEC initiative promoting market-oriented research activities by providing co-working lab and office space to help high-potential initiatives funded by external investment capital to go further and faster to the market.

The Open Innovation Lab hosts research units with a clear objective to reach the market as soon as possible and take advantage of IBEC's rich environment of knowledge and science provided by its research groups, its high-tech facilities, national and international networks, and strategic alliances with hospitals and capital and industrial partners.

The initiative is open to companies and investors interested in setting up a new research and development unit with a clear market objective. The research unit is financed by a company or an investor and is allocated in IBEC's facilities. The goal is to build an ecosystem in bioengineering that empowers entrepreneurial scientists to grow quickly, while maximizing capital efficiency.

IBEC's initiative is based on a new wave of 'innovative ecosystems' being pioneered at Princeton and in Norway, to name just two, and is one of the most important initiatives of IBEC's new Strategic Plan. It's fully aligned with our mission to foster innovation, collaboration and entrepreneurship by supporting early stage high-potential projects and bringing our basic and applied research results more quickly to the market.

The first Open Innovation Lab research unit at IBEC is Bioengineering for Reproductive Health, led by Dr. Samuel Ojosnegros, with four years of financing to the tune of €1.4m from Scranton Enterprises B.V., an investment association based in the Netherlands.

The unit will develop a new system for assisted reproduction programmes to predict the success rate of embryos for implantation. Selecting embryos is a critical aspect of this treatment that at the moment is left largely to chance, leading to disappointment and suffering for many patients.

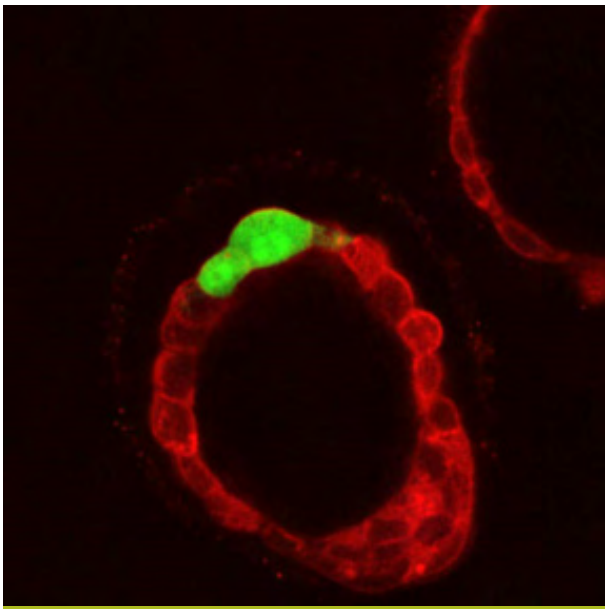
OPENLAB - Bioengineering in reproductive health

Samuel Ojosnegros

Our lab studies the development of human and mouse embryos. Our goal is to understand the mechanisms controlling mammalian embryo implantation and use that information to provide solutions that improve in vitro fertilization (IVF).

The embryonic development of humans (and mammals in general) requires the implantation of the embryo into the walls of the mother uterus. Implantation involves the attachment of the embryo to the uterine lining, termed endometrium, and the invasion of the tissue to form the placenta. This process is crucial for natural conception and especially for in vitro fertilization (IVF) as only 25% of IVF embryos successfully implant into the mother uterus' and develop to term. However, despite the central role of implantation in human fertility, the process is still elusive to experimentation because of its inaccessibility.

In our lab we use bioengineering methods to create 3D environments that support embryonic development outside of the mother uterus. Our systems are accessible to imaging tools which allow us to interrogate the genetics, metabolomics and mechanics of the embryo in a high throughput manner. Using our systems we are capable to (i) improve embryo culture conditions and (ii) diagnose embryos with improved implantation potential. Due to the high translational component of our research, we have established collaboration contracts with the pharma industry, hospitals and venture capital to bring our technology to the clinics and the market. Our Open Lab is a multidisciplinary environment where biologists, biophysicists, clinicians and business developers synergize to create a unique environment shaped by science and entrepreneurship.



Transgenic mouse embryo at blastocyst stage expressing the fluorescent protein tdTomato in the membrane and pa GFP in few selected cells.

Open Lab: Bioengineering in Reproductive Health

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Bioengineering in reproductive health

Senior researcher
Anna Seriola

Lab technician
Mar Casals

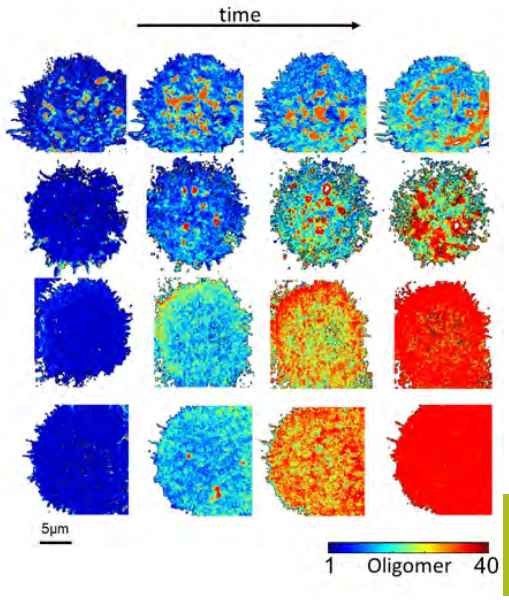
Business strategy
Jorge Fuentes

established collaboration contracts with the pharma industry, hospitals and venture capital to bring our technology to the clinics and the market. Our Open Lab is a multidisciplinary environment where biologists, biophysicists, clinicians and business developers synergize to create a unique environment shaped by science and entrepreneurship.

Enhanced Number and Brightness a novel Imaging technique reveals protein dynamics in live cells

Proteins continuously interact with other proteins in the cell yet revealing these interactions in live-cell microscopy is technically challenging. Using statistical tools we designed the Enhanced Number and Brightness method , which quantifies and maps protein aggregation in live cells from high resolution movies.

Several fluorescence microscopy methods can be used to measure protein interactions in cells. However, most of the methods struggle to capture both the diversity of these interactions across the entire cellular area and their dynamics over time. To overcome these limitations, we enhanced the spatiotemporal resolution of Number and Brightness, a spectroscopy method that transforms fluorescence fluctuations into protein aggregation values. The Enhanced Number and Brightness method implements two algorithms, the first one uses statistical tools to extract the distribution of protein oligomers (monomers, dimers, trimers and so on) in single pixels, thus revealing protein diversity across an entire cell image. The second one corrects the fluorescence intensity loss due to continuous light exposure, which enables measurements over prolonged periods of time. By combining these two algorithms, Enhanced Number and Brightness allows extended live imaging, providing dynamic maps of protein oligomerization overlaid on top of the corresponding cell image.



Enhanced Number and Brightness provides oligomerization maps (color-coded according to reference bar) during time-lapse movies. The image shows from left to right the dynamics of Eph receptor aggregation after stimulation with the ligand Ephrin. Each row depicts a cell stimulated with different types of ligands (i.e. soluble, surface-bound etc.).

EQUIPMENT

- Micromanipulation-microinjection station
- Embryo biopsy laser
- Embryo culture laboratory
- Genome editing
- In vitro fertilization
- ICSI
- Cell culture laboratory
- 3D cell culture
- Advanced live imaging: photoconversion, 3D imaging, light scattering, spectroscopy
- Image analysis workstation

Associated Researchers

Associated Researchers are university professors seconded to IBEC with a bilateral agreement. They are based in the university premises and working on topics that are of interest, or complementary, to IBEC research areas.

IBEC Associated Researchers participate in IBEC´s scientific strategy, academic activities and support initiatives. They also have the option to submit project proposals and scientific papers with IBEC affiliation. Their recruitment is carried out according to several criteria such as scientific excellence and alignment with IBEC´s institutional strategy. Associated Researchers are approved by the International Scientific Committee, which also evaluates their performance on a regular basis.

MARINO ARROYO is is Full Professor at the Universitat Politècnica de Catalunya (UPC), where he is a member of the Laboratory of Computational Methods and Numerical Analysis Group (LaCaN).

Before joining the UPC, he obtained a PhD from Northwestern University, was a postdoctoral scholar at the California Institute of Technology (Caltech) and a long-term visitor at the Institute for the Mathematics and its Applications (University of Minnesota). He has been awarded the O. C. Zienkiewicz Award for Young Scientists in Computational Engineering Sciences by ECCOMAS (2010), two ICREA Academia Awards (2009, 2015), and the ASME/BOEING Structures and Materials Award (2003).

He has also been the Timoshenko Visiting Scholar at Stanford. He was awarded a ERC-Starting in 2009 and a ERC Consolidator Grant in 2016. In 2016 he came third, alongside IBEC group leader and ICREA research professor Xavier Trepat, in the La Vanguardia Science Award for their groups' research that was published in *Nature Materials*.

His research goal is to develop theories and computational methods to understand the small-scale mechanics of materials and biological systems, with a recent emphasis on cell and tissue mechanobiology and bio-inspired materials.

ALÍCIA CASALS led the Robotics Group at IBEC from 2008 to 2015.

While at IBEC she began a spin-off company with the UPC, Rob Surgical Systems, which aims to develop a minimally invasive robotic station for surgery, Bitrack, and also worked alongside researchers at the Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau and at the UPC on the development of Surgitrainer, a training platform for laparoscopic surgery. The group was awarded funding for projects such as HYPER, which aims to develop new treatments in neurorehabilitation and help with patients' mobility, and RecerCaixa funding for InHANDS ("Robòtica interactiva per a l'assistència humana en l'entorn domèstic") and "Desenvolupament d un sistema robòtic de baix cost d ajut a la rehabilitació de la marxa per a nens amb transtorns motors greus".

Alícia was recognized for her work as a research scientist in the "16 Científiques Catalanes" exhibition being organized by the Catalan Association of Science Communication (ACCC) in 2010, and immortalised as a notable representative of the field of industrial engineering in the educational card game "La paciència és la mare de la ciència" by "IEC's Secció de Ciències I Tecnologia". In 2015 she received the *Fem Talent Forum Award* in Barcelona.

Associated Researchers

MARIA-PAU GINEBRA is Full Professor in the Department of Materials Science and Metallurgy and director of the Biomaterials Division of the Research Centre for Biomedical Engineering at the Technical University of Catalonia (UPC) in Barcelona, Spain, where she leads the Research group on Biomaterials, Biomechanics and Tissue Engineering. She has received numerous awards, amongst them the ICREA Academia Award in 2008 and 2013 and 2018 and the Narcis Monturiol Medal in 2012 from the Generalitat de Catalunya, and the Racquel LeGeros Award, from the International Society for Ceramics in Medicine, for her contribution to calcium phosphate research, in 2013.

Her research interests include the design and development of new biomaterials for bone regeneration, bone tissue engineering and drug delivery. Her research team has made significant contributions in the processing and characterisation of a new generation of calcium phosphate-based materials which mimic bone extracellular matrix, including calcium phosphate cements and foams, incorporating synthetic or natural polymers, and/or biologically active molecules. She is involved also in new biofabrication strategies, including injectable scaffolds for bone tissue engineering, bioinspired substrates and 3D printing of regenerative medical implants. She has been involved in numerous national and European research projects and participated in the organisation of scientific events in the area of biomaterials and bioceramics. She is author of more than 150 articles in peer-reviewed International journals as well as of 9 patents. In 2013 she founded the spin-off company *Mimetis Biomaterials*.

ANTONIO JUÁREZ led the Microbial Biotechnology and Host-Pathogen Interaction group at IBEC between 2007 and 2015.

The group's focus was the protein– protein and protein–DNA interactions that play key roles in the ability of virulent bacteria to adapt to the host environment and cause disease, with a particular interest in finding ways to tackle the resistance of bacteria to antibiotics. During his time at IBEC, he and colleagues from the UB and IRB identified the strategy used by enterobacteria to acquire resistance and pathogenicity (Baños, R.C. et al. (2009), PLoS Genet), and worked together with IBEC's Nanoscale Bioelectrical Characterization group to demonstrate the potential of electrical studies of single bacterial cells (Esteban-Ferrer, D. et al., (2014), ACS Nano).

The group also embarked on a technology transfer venture together with two biopharmaceutical companies, CZV Veterinaria and MEVET, to obtain strains of Salmonella with weakened virulence, which can then be used to develop a vaccine to reduce the incidence of the infection in poultry farms.

His currents research projects are: (i) the analysis of enterobacterial genomes to better understand bacterial virulence and to identify new targets for novel vaccines, and (ii) the development of a novel approach to combat plasmid-mediated antibiotic resistance.

PUBLICATIONS

Alícia Casals

- Miquel, J. et al (2018). Retaining or excising the supraspinatus tendon in complex proximal humeral fractures treated with reverse prosthesis: a biomechanical analysis in two different designs. Archives of Orthopaedic and Trauma Surgery, 138 (11): 1533-1539

Maria-Pau Ginebra

- Sadowska, J. M. et al (2018). Effect of nano-structural properties of biomimetic hydroxyapatite on osteoimmunomodulation. Biomaterials, 181 318-332
- Sadowska, J. M. et al (2018). In vitro response of mesenchymal stem cells to biomimetic hydroxyapatite substrates: A new strategy to assess the effect of ion exchange. Acta Biomaterialia, 76 319-332
- Raymond, S. et al (2018). Accelerated hardening of nanotextured 3D-plotted self-setting calcium phosphate inks. Acta Biomaterialia, 75 451-462

RALPH G. ANDRZEJAK is director of the Nonlinear Time Series Analysis Group at the Department of Information and Communication Technologies at the Universitat Pompeu Fabra (UPF) in Barcelona. His department has recently been awarded as a "Maria de Maeztu Unit of Excellence" by the Spanish Ministry of Economy and Competitiveness (MINECO).

He pursues two parallel research tracks. On the one hand, he develops innovative nonlinear signal analysis techniques. These techniques aim, for example, at the detection of non-random structure in complex dynamics or the characterization of interactions in networks of dynamics. On the other hand, he applies these techniques to real-world biomedical signals. Here an emphasis is placed on different types of electrophysiological recordings from epilepsy patients.

Prof. Andrzejak was born in Germany and has a degree and PhD in physics (University Bonn, Germany). During his career he was affiliated with the Neurophysics group of K. Lehnertz and C.E. Elger (Department of Physics and Department of Epileptology, University Bonn, Germany), the Neurodynamics research group of S.J. Schiff (George Mason University, Fairfax, USA), the Complex Systems research group of P. Grassberger (Research Centre Jülich, Germany), and the Computational Neuroscience group of G. Deco at the Department of Information and Communication Technologies at the Universitat Pompeu Fabra. Since 2011, he is a tenured associate professor at this Department.

Ralph G. Andrzejak has published over 60 publications in leading journals of physics, neuroscience, neurology, and engineering.

His work has received more than 2400 citations (h-index: 23; ISI Researcher ID: H-7923-2012). In Google Scholar the publications of Prof. Andrzejak reach more than 4500 citations (h-index: 30). He is principal investigator of several prestigious research projects receiving funding from Spanish, German and European Institutions.

■ Barba, A. et al (2018). Osteogenesis by foamed and 3D-printed nanostructured calcium phosphate scaffolds: Effect of pore architecture. Acta Biomaterialia, 79 135-147

■ Diez-Escudero, A. et al (2018). Heparinization of beta tricalcium phosphate: Osteo-immunomodulatory effects. Advanced Healthcare Materials, 7 (5): 1700867

■ Guillem-Marti, J. et al (2018). Recombinant fibronectin fragment III8-10/polylactic acid hybrid nanofibers enhance the bioactivity of titanium surface. Nanomedicine, 13 (8): 899-912

■ Qi, Y. et al (2018). Effects of molecular weight and concentration of poly(acrylic acid) on biomimetic mineralization of collagen. ACS Biomaterials Science & Engineering, 4 (8): 2758-2766

■ Hoyos-Nogués, M. et al (2018). All-in-one trifunctional strategy: A cell adhesive, bacteriostatic and bactericidal coating for titanium implants. Colloids and Surfaces B: Biointerfaces, 169 30-40

■ Khurana, K. et al (2018). Plasma polymerized bioceramics for drug delivery: Do surface changes alter biological behaviour? European Polymer Journal, 107 25-33

Antonio Juárez

■ Prieto, A. et al (2018). Evolution of bacterial global modulators: Role of a novel H-NS paralogue in the enteroaggregative escherichia coli strain 042. mSystems, 3 (3)

■ Hüttener, M. et al (2018). Stringent response and AggR-dependent virulence regulation in the enteroaggregative escherichia coli strain 042. Frontiers in Microbiology, 9 (717): Article 717

■ Hüttener, M. et al (2018). Tetracycline alters gene expression in Salmonella strains that harbor the Tn10 transposon. Environmental Microbiology Reports, 10 (2): 202-209

Ralph G. Andrzejak

■ Andrzejak, R. G. et al (2018). Mean field phase synchronization between chimera states. Chaos: An Interdisciplinary Journal of Nonlinear Science, 28 (9): 091101

Marino Arroyo

■ Latorre, E. et al (2018). Active superelasticity in three-dimensional epithelia of controlled shape. Nature, 563 (7730): 203-208

Core Facilities
Isabel Oliveira

IBEC provides its scientists with extensive research facilities and a scientific–technical infrastructure distributed over interdisciplinary open lab spaces. It is designed and managed to facilitate investigation and promote the cooperation and exchange of knowledge between IBEC researchers from different fields of expertise.

IBEC Core Facilities are organized into six blocks: Labs Layout and Logistics; Common Core Basics; BioSpace Lab; ChemSpace Lab; MicroFabSpace Facility and Microscopy Characterization Facility.

LABS LAYOUT AND LOGISTICS

In 2018, IBEC has refurbished 292.4 m^2 at the Barcelona Scientific Park (PCB), including laboratory and administration spaces. Also, we've reorganized some spaces at PCB and we've made a laboratory closure at Belltvige - UB Campus.

Furthermore, with the purpose of installing new scientific equipment, refurbishment of several spaces has been carried out during the year.

JANUARY – Reorganization of IBEC's spaces at Tower I building. The Institute leaves 261.2 m^2 and Dr. Santiago Marco's group is relocated in 81.56 m^2 of dry laboratory space.

MAY – Prof. George Altankov has retired and we've closed his laboratory at Bellvitge - UB Campus. All his equipment has been relocated at IBEC's spaces at the Barcelona Scientific Park.

JUNE - IBEC's administration suffers a space reorganization and expanded to a new 60.30 m^2 space located in the administration building (PCB). This new space is occupied by the Finances Unit.

JULY – Prof. Silvia Muro, new senior/ICREA group leader, opened her 125.7 m^2 laboratory in the Clúster I building (PCB). The laboratory was designed, considering the research activity requirements of the group. Several spaces dedicated to specific activities, for Instance, chemistry, cell cultural and confocal microscopy were configurated.

SEPTEMBER - Dr. Benedetta Bolognesi, new junior group leader, opened her 56.55 m^2 laboratory in the Hélix building (PCB).

DECEMBER – a new laboratory concept was opened - Open Innovation Lab. 49.85 m^2 were set up to house the Bioengineering for Reproductive Health. led by Dr. Samuel Ojosnegros.

IBEC's new Open Innovation Lab.

MicroFabSpace and Microscopy Coordinator
Teresa Galán

MicrofabSpace and Microscopy Technicians
Marina Cazorla
Judit Linacero

MicroFabSpace Assistant
Alícia Nadal

Research Technician
Claudia Di Guglielmo

Laboratory Technician
Ramona Bravo
Miriam Funes
Laura Gómez
Inma Moreno
Sandra Segura

Administrative Assistant
Tania Bordoy

COMMON CORE BASICS

Manage the general maintenance and organization of 2228.35m^2 of IBEC's wet labs (18 IBEC research groups) in the PCB. To keep the overall standard organization of the labs and facilitate the research, the following services are included:

- Inform and train the new incomers about the organization and safety inside IBEC labs, guiding them through the different spaces.
- Management, preventive and corrective maintenance of shared areas inside the labs and common equipment distributed all over IBEC laboratories.
- Reception, documentation (purchase related paperwork and databases/MSDS) and storage of the chemicals (following chemical incompatibility criteria) purchased by the research groups.
- Reception and documentation (purchase related paperwork and inventory databases) of the equipment bought by the research groups.
- Management of an "in house shop", with about 76 laboratory consumables available, which in 2018 has dealt with 1290 internal lab material orders. The objective is, on the one hand, to obtain laboratory consumables at low cost, due to high amount orders, and on the other hand, to optimize the in lab storage space for this type of consumables, as there is no stock accumulated in the laboratories.
- Lab coats laundry management.
- Organization and preparation of laboratories waste for removal. Advice on doubts that may arise regarding the classification of the residues.

Apart from routine laboratory equipment, IBEC's Core Facilities provide additional sophisticated, state-of-the-art equipment to support the groups' research.

Small equipment available:

Scales, heating baths, thermoblocks, thermomixers, centrifuges, magnetic stirrers with or without heater, platform shakers, ultrasonic baths, pHmeters, conductimeter, incubators, ovens, water purification systems, UV tip cleaner, sterilize miniclave, puller machine, etc.

Specific routine laboratory equipment available:

- Chromatography System Biologic LP – Bio-Rad
- Spectrophotometer UV-Visible – Shimadzu
- Spectrophotometer – Nanodrop
- Multimode microplate reader Infinite M200 Pro – Tecan
- Microplate Reader Benchmark Plus – Bio-Rad
- StepOnePlus Real Time PCR System – Applied Biosystems
- DNA Engine Thermal Cycler – Bio-Rad
- T100 Thermal Cycler – Bio-Rad
- GeneAmp PCR System 9700 - Applied Biosystems
- ImageQuant LAS 4000 mini – GE Healthcare
- GelDoc XR+ System – Bio-Rad

LABORATORIES

BIOSPACE LAB

Common space dedicated to work with primary and cell line cultures and 3D bioprinting. It is equipped with several Class-II biosafety cabinets and Co2 incubators, with one incubator prepared for complex experiments with cells that include extra equipment, and routine equipment for cell culture. Due to the demand of "alternative" Co2 incubators, suitable to carry out experiments with cells and devices with complex configurations, in September 2018, another large incubator was added to the space and dedicated to this type of experiments. Also, researchers have access to an inverted microscope and a stereomicroscope, both with epifluorescence option and camera for image caption. During 2018, 108 IBEC researchers from 11 groups have used this space.

3D bioprinting is a hot topic in the Strategic Plan of the Institute in the areas of regenerative medicine and tissue engineering. Our 3D bioprinter allows the printing of different types of biomaterials (polymers, abrasive viscous substances, hydrogels loaded with cells and solutions) in a coordinated way, generating complex multi-material 3D scaffolds and therefore closer to biological tissues. The applications of this 3D constructs span from 3D cellular models for drug screening (i.e. dermis), scaffolds for regenerative medicine and, at a

more advanced stage, organ-printing. In collaboration with Hospital Clinic de Barcelona (Department of Pathology), within the CaixaImpulse project, we are developing 3D bioprinted structures useful to optimized cancer diagnosis.

At present, 24 IBEC researchers from 7 groups are developing their 3D biostructures in this 3D bioprinter.

CHEMSPACE LAB

Shared space prepared to carry out 'heavy' organic/inorganic chemical synthesis. It's an isolated space furnished with several chemical fume hoods, equipped with argon and nitrogen, gases necessary to perform chemical reactions in a controlled atmosphere. Also, routine specific equipment for chemical synthesis is available. IBEC groups that are developing innovative bioactive compounds and biomaterials are intensive users of the facility.

MICROFABSPACE

Versabile esearch facility featuring 90m2 of class 10,000 cleanroom space, offering state-of-the-art equipment for the microfabrication and characterization of biomedical related devices and structures.

Presently, the facility provides advanced research support that includes the design, development and analysis of devices, up-to-date processes, materials and more. Researchers may use the facility to develop their innovative ideas in the fields of bioengineering, BioMEMS, materials science, tissue engineering and microfluidics.

This facility is open to potential users from other public institutions and private companies.

In 2018, we opened a new service - the 3D Pinter. This printer uses photopolymerizable resins to fabricate plastic parts. If researchers need to customize a small plastic piece, such as tub fitting or a small part that has broken from a piece of their equipment, they can make it using this kind of technique.

Services:

- Access to 10 000 class cleanroom.
- Technical support and training on equipment and processes as self-user.
- Custom fabrication and characterization services assisted by scientific personnel (quotation required).

3D bioprinted structures.

Structures obtained with the new 3D-pinter.

Fabrication:

- Design and fabrication of customized microfluidic molds (SU-8) and microfluidic chips (PDMS replica)
- Design and fabrication of 3D submillimetre structures
- Design and fabrication of high-resolution nanostructures by E-beam lithography
- Design and fabrication of Cr photomasks for photolithographic processes
- Design and fabrication of micro-structures by direct laser lithography (DWL)
- Thin film deposition by thermal evaporation, electron beam evaporation and sputtering
- Design and fabrication of microelectrodes.

Characterization:

- Surface topographic analysis using optical interferometry and mechanical profilometry
- Optical characterization of samples with bright and dark field microscopy
- Contact angle measurements of wettability properties of surfaces

Equipment:

- E-beam Lithography (EBL) Elphy Puls - Raith
- UV-Photolithography Mask-aligner MJB4 – SÜSS Microtec
- Direct Write Laser 66FS – Heidelberg Instruments
- Evaporator and Supttering Univex 450B – Oerlikin Leybold Vacuum
- Spin-coaters – Laurell Technologies Corporation (2 units)
- Plasma Cleaner PDC-002 – Harrick Scientific Corporation
- 3D Printer - Solus DLP - Reify 3D (NEW)
- Chemical Bath - Quimipol
- Interferometer WYCO NT1100 – Veeco Instruments
- Profilometer DEKTAK 6M – Veeco Instruments
- Optical microscope equipped with camera for samples inspection BX51RF – Olympus
- Stereo microscope for samples inspection - Olympus
- Contact angle measure equipment OCA15Plus - Dataphysics

Some data related to MicroFabSpace users

During 2018, 112 researchers from seventeen IBEC groups, 55 researchers from 10 other public institutions (included 2 international public Institutions), and 7 from 4 private companies have used as a self-user or order a service available at the MicroFabSpace facility.

MICROSCOPY CHARACTERIZATION

This facility is composed of a variety of microscopy equipment, useful for very different applications in the biomedical field. With these techniques IBEC researchers can acquire Images and analyse structures, from single molecules all the way to the nanoscale of living cell. The service is in different spaces and managed separately. Therefore, we offer microscopes managed centrally by Core Facilities, which are opened to other public and private institutions. There are also other instruments managed by IBEC groups that open 30% of their usage time to other IBEC researchers.

3D Printer Solus DLP.

Core Facilities

Equipment & Services

■ Ultra-High-Resolution Field Emission Scanning Electron Microscopy (SEM) – Nova NanoSEM FEI.

• Training as a self-user on the use of the SEM microscope (only for IBEC researchers).

• SEM morphological and topographical characterization.

■ Preparation of SEM samples:

• Gold coating service for high resolution Inspection of Insulating samples.

• Chemical fixation of biological samples.

■ This microscope is open to potential users from other public institutions and private companies.

■ Confocal Microscope with Spectral Detection LSM 800 – Zeiss

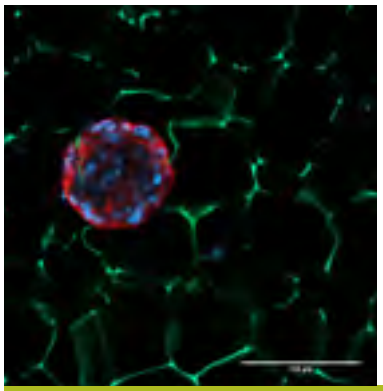
• Training as self-user (only for IBEC researchers)

• Confocal and fluorescence imaging.

■ Topographical (SEM) and fluorescence (confocal) combined studies.

■ Bio-Atomic Force Microscope (Bio-AFM) – JPK. Managed by Gabriel Gomila's group

■ Stochastic Optical Reconstruction Super Resolution Microscope (STORM) – Nikon. Managed by Lorenzo Albertazzi's group.



Confocal image of a pancreas island into cryagel. Image provided by Ferran Velasco & Javier Ramón (Biosensors for Bioengineering group).

Some data related to Microscopy Characterization users

During the last year, 97 researchers from thirteen IBEC's groups, 18 researchers from 7 other public institutions, and 11 from 7 private companies have used the Microscopy Characterization facility as a self-user or ordered one of its services.

MICROFABSPACE AND MICROSCOPY CHARACTERIZATION EXTERNAL USERS IN 2018

■ Advanced Nanotechnologies S.L.

■ BCN Peptides, S.A.

■ Bio-model

■ GP-Pharm, S.A

■ Infinitec Activos S.L.

■ Institut Químic de Sarrià (IQS)

■ Stat-Diagnostica and Innovation S.L.

■ Fundació Centre de Regulació Genòmica (CRG)

■ Fundació Bosch i Gimpera (FBG)

■ Institut Català de Nanociència i Nanotecnologia (ICN2)

■ Institut de Biologia Molecular de Barcelona (IBMB-CSIC)

■ Institut de Quimica Avançada de Catalunya (IQAC-CSIC)

■ Instituto de Ciencias Fotónicas (ICFO)

■ Universitat Autonòma de Barcelona (UAB)

■ Universitat de Barcelona (UB)

■ Universitat Politècnica de Catalunya (UPC)

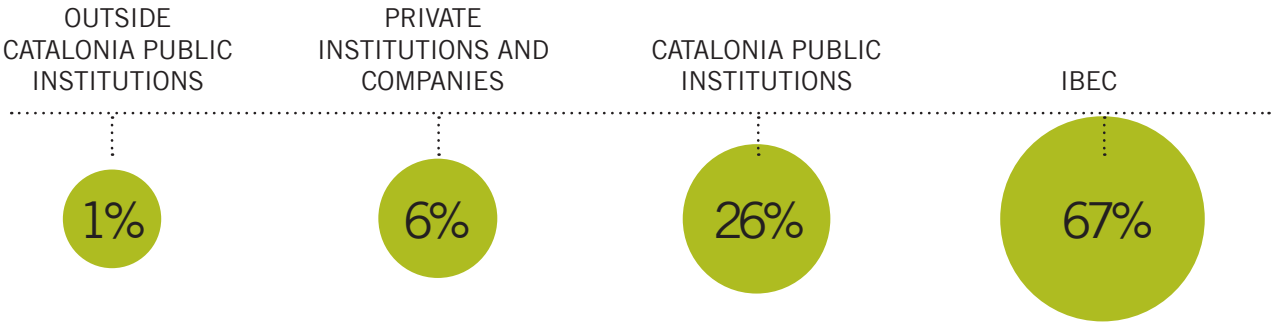
■ Universitat Rovira I Virgili

■ Universidad del País Vasco

■ Swiss Federal laboratories for Materials Science and Technology (EMPA)

■ Max Planck Institute for Brain Research

MicroFabSpace and Microscopy Characterization Services users in 2018



ACTIVITIES DURING 2018

Participation in the program Bojos per la Ciència - Bioenginyeria from Fundació Catalunya La Pedrera, with a theoretical/practical seminar titled "Buenas Prácticas de laboratorio"

Invited talk at the Banc de Sang I Teixits, entitled “3D Bioprinting: Engineering complex tissues with soft materials".

Participation with a talk titled "3D Bioprinting: Engineering complex tissues with soft materials" in the biotechnology degree at the University of Barcelona.

In collaboration with Technology Transfer Unit, we have participated in the exposition IN3DUSTRY held in Barcelona with 3D bioprinted gelatine samples reproducing human hear cartilage and skin.

Participation in IBEC Symposium poster session presenting the MicroFabSpace and Microscopy Characterization services.

Organization of the workshop ‘Good practices in a multi-disciplinary laboratory’ held at IBEC and aimed at young scientists and students at the institute. The objective was to acquire the good practices necessary in a laboratory to ensure the highest quality of results.

Participation in the master of Quimica de Materiales Aplicada at the University of Barcelona entitled "Applications of secondary Ion mass spectrometry".

RESEARCH PROJECTS

3D bioprinted tissue-like cores for cancer diagnostics. The goal of the project, to take advantage of 3D bioprinters to create 3D tissue-like structures containing biomarkers that can be used as quality controls in histopathological analysis in companion diagnostics kits.
PI: **Mateu Pla / Claudia Di Guglielmo / Xavier Puñet**
CaixaImpulse 2017-2019

The MicroFabSpace and Microscopy Characterization (only SEM) are also an active member of the ICTS (Infraestructuras Científicas y Técnicas Singulares) map as part of NANOBIOSIS (Infraestructuras Integradas de Producción y Caracterización de Nanomateriales, Biomateriales y Sistemas en Biomedicina), an integrated platform for research-oriented medical applications (U7 – Nanotechnology Unit). As an integrating unit in the ICTS-NANBIOSIS, our services have achieved participation in a European project H2020, within the call DT-NMBP-02-2018 (Open Innovation Test Beds for Safety Testing of Medical Technologies for Health (IA)), entitled "SAFETY TESTING IN THE LIFE CYCLE OF NANOTECHNOLOGY-ENABLED MEDICAL TECHNOLOGIES FOR HEALTH" (SAFE-N-MEDTECH) "

Notes

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